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Sex-specific clinical outcomes of impaired glucose status: A long follow-up from the Tehran Lipid and Glucose Study

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Abstract

Aims: To investigate the sex-specific associations of prediabetes with major clinical outcomes including incident type 2 diabetes, chronic kidney disease, hypertension, coronary heart disease, stroke and all-cause mortality.

Methods: Among 8498 Iranian adults from the Tehran Lipid and Glucose Study, aged ≥30 years and without diagnosed type 2 diabetes, gender-interactions were assessed for each outcome, followed by sex-separated multivariate-adjusted Cox proportional hazard models to calculate hazard ratios and 95% confidence intervals (CIs) of different prediabetes categories, including impaired fasting glucose (IFG), defined by the American Diabetes Association (ADA) and World Health Organization (WHO), as fasting plasma glucose of 5.6–6.9 mmol/L and 6.1–6.9 mmol/L, respectively, and impaired glucose tolerance, defined as 2-h post challenge plasma glucose of 7.8–11 mmol/L.

Results: Sex-specific associations existed for men between IFG-ADA and chronic kidney disease (hazard ratio: 1.28, 95% CI 0.99–1.65; $p_{interaction} = 0.008$) and between IFG-WHO and stroke (hazard ratio: 2.15, 95% CI 1.08–4.27; $p_{interaction} = 0.21$); and for women between IFG-ADA and hypertension (hazard ratio: 1.24, 95% CI 1.04–1.48; $p_{interaction} = 0.06$) and between impaired glucose tolerance and coronary heart disease (hazard ratio: 1.57, 95% CI 1.14–2.16; $p_{interaction} = 0.05$). Among both genders, all prediabetes definitions were associated with type 2 diabetes but none with mortality.

Conclusions: The hazards of prediabetes definitions may differ between genders depending on the outcome of interest. IFG-WHO among men and impaired glucose tolerance among women are particularly important because of their association with incident stroke and coronary heart disease, respectively. Considering these sex differences could improve personalized management of prediabetes.

Keywords

Prediabetic state, impaired fasting glucose, impaired glucose tolerance, hypertension, renal insufficiency, cardiovascular disease

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Introduction

Prediabetes, as a high-risk state for developing diabetes, has been identified by the World Health Organization (WHO) as impaired fasting glucose (IFG), defined as fasting plasma glucose (FPG) 6.1–6.9 mmol/L or impaired glucose tolerance (IGT), referred to as 2-h post challenge glucose (2h-PCPG) 7.8–11 mmol/L, among non-diabetic individuals.[1] The American Diabetes Association (ADA) agrees with the WHO

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definition of IGT, yet recommends a lower cut-point of FPG, 5.6–6.9 mmol/L, to define IFG.[2] Iran, with more than 4% incidence rate of prediabetes,[3] holds a high-risk adult population for this condition.

Observational studies have investigated the association of prediabetes with several major outcomes, including chronic kidney disease (CKD),[4] hypertension,[5,6] cardiovascular disease (CVD) and mortality;[7] however, the results have been inconsistent. Gender distribution may be a source of disparity in these studies besides other factors such as different definitions of prediabetes or ethnicity.[8] Gender difference has been observed previously in the consequences of insulin resistance and type two diabetes (T2D).[9,10] Although the underlying mechanisms are not fully understood, differences in both metabolic and behavioral factors may play a role.[11] Regarding prediabetes, it has been shown that the prevalence of different phenotypes varies between men and women;[11] yet few studies have analyzed sex-specific clinical outcomes.[4,7] Moreover, the health outcomes of prediabetes may vary between IFG and IGT phenotypes, due to their different etiologies and pathogenesis,[8] or by applying different IFG cut-points, as observed in previous studies.[12]

Although the Middle East is a high risk region for prediabetes and its potential complications,[3,13,14] the majority of related studies are attributed to the United States, Europe or East Asia.[4,7,15]

Extending the previous literature, here we aim to investigate the associations between different definitions of prediabetes with six major outcomes, including T2D, hypertension, CKD, coronary heart disease (CHD), stroke and all-cause mortality, separately among men and women from the Tehran Lipid and Glucose Study (TLGS), a population-based prospective cohort from the Middle East.

Methods

Study design and setting

The TLGS is an ongoing community-based prospective cohort study on a representative population of Tehran, the capital of Iran, with the aim to investigate the risk factors for non-communicable diseases. Participants have been recruited in phases I (1999–2001) and II (2002–2005) and data collection has continued at approximately three-year intervals in the follow-up phases (i.e. phase III: 2005–2008, phase IV: 2008–2011, phase V: 2011–2015). Details of the design have been explained elsewhere.[16] For this study, 9752 participants aged ≥ 30 (8071 enrolled in phase I and 1681 enrolled in phase II) were selected.

Study population

Figure 1 illustrates the details of the study population, including the outcome-specific exclusion criteria, response rates and follow-up duration. As shown, initially, subjects with history of taking glucose lowering medication ($n = 537$) or missing data on 2h-PCPG ($n = 717$) were excluded, leaving 8498 participants. Then, separate exclusion criteria were applied for the analysis of each outcome. Accordingly, for the analysis of incident T2D, after excluding those with undiagnosed T2D at baseline ($n = 66$), missing baseline values of any covariates used in T2D models ($n = 782$), or no follow-up after baseline ($n = 1439$), 5615 participants remained. For CKD analysis, after excluding those with prevalent CKD ($n = 1694$), missing covariates ($n = 226$) or no follow-up ($n = 1092$), 5486 participants remained. For hypertension analysis, after excluding those with prevalent hypertension ($n = 2069$), missing covariates ($n = 220$) or no follow-up ($n = 1014$), 5195 participants remained. For CHD and stroke analyses, after excluding those with prevalent CVD ($n = 430$), missing covariates ($n = 253$) or no follow-up ($n = 677$), 7138 participants remained. Finally, for mortality, those with missing covariates ($n = 256$) or no follow-up ($n = 745$) were excluded, leaving 7497 participants for analysis. Participants were followed up until January 2015. Response rates ranged from 71.65% (for T2D) to 96.69% (for mortality). Informed written consent was obtained from all participants and the study was approved by the Ethical Committee of Research Institute for Endocrine Sciences.

Clinical and laboratory measurements

A trained nurse obtained data including demographics, past medical and drug history, family history of T2D and CVD, and smoking status using a questionnaire. Details on measuring anthropometrics and blood pressure have been explained elsewhere.[16] Blood samples were collected between 07:00 h and 09:00 h, after a 12–14 h fast, and analyzed on the same day. For subjects without history of taking glucose-lowering medication, an oral glucose tolerance test was performed, measuring plasma glucose 2 h after administrating 75 g glucose orally. Further details of laboratory measurements including FPG, 2-h PCPG, total cholesterol, triglycerides, high-density lipoprotein cholesterol and serum creatinine have been reported previously.[16] Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[17]

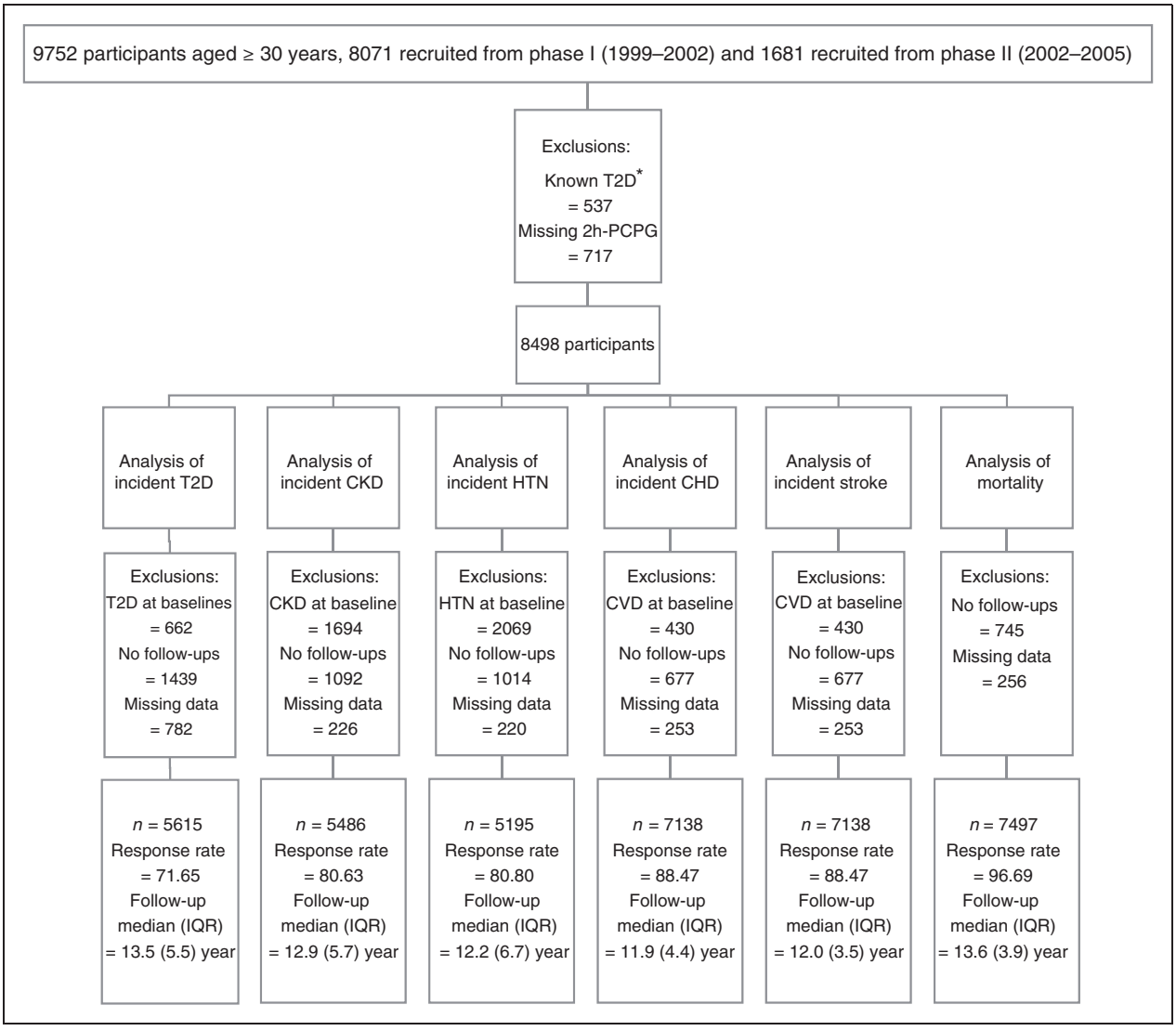

Figure 1. Flowchart of the study population, Tehran Lipid and Glucose Study, 1999–2015.
*Known T2D was defined as positive history of taking glucose-lowering medication at baseline.
T2D: type 2 diabetes; 2h-PCPG: 2-h post challenge plasma glucose; HTN: hypertension; CHD: coronary heart disease; CKD: chronic kidney disease; CVD: cardiovascular disease; IQR: interquartile range

Definition of terms

For details please see Supplementary Material Table 1 online. Glycemic status categories were defined for subjects without known T2D (i.e. taking glucose-lowering medication at baseline), as normoglycemia (reference group), prediabetes, and undiagnosed diabetes. Prediabetes phenotypes included IFG-ADA ($5.6 \leq$ FPG < 7 mmol/L), IFG-WHO ($6.1 \leq$ FPG < 7 mmol/L) or IGT ($7.8 \leq$ 2h-PCPG < 11.0 mmol/L). Undiagnosed T2D was defined as FPG ≥ 7.0 mmol/L or 2h-PCPG ≥ 11.0 mmol/L. Positive family history of premature CVD equaled history of CHD/stroke in a male first-degree relative before 55 years old or female first-degree relative before 65 years old. Positive family history of diabetes equaled having a diabetic first-degree relative. Education levels < 6 years (reference group), 6–12 years, and >12 years of formal education. Smoking status was defined as current smoker versus non-smoker (reference group). Body mass index (BMI) was calculated as weight (kilograms) divided by height (centimeters squared). Waist-to-hip ratio was calculated as waist circumference (centimeters) divided by hip circumference (centimeters). T2D was defined as FPG ≥ 7.0 mmol/L or 2h-PCPG ≥ 11.0 mmol/L or taking glucose-lowering medication(s). CKD was

defined as eGFR <60 mL/min per 1.73 m^2. Hypertension equaled systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure (DBP) $\geq$ 90 mmHg or taking antihypertensive medication(s). For data collection on cardiovascular outcomes and mortality, participants were followed up through annual phone interviews by a trained nurse regarding related medical events. Complementary information on each medical event was gathered by a trained physician during a home visit, or from hospital records, death certificates, forensic medical reports or verbal autopsy, as required.[16] CHD and stroke were diagnosed by the International Classification of Diseases, 10th Revision Rubric (CHD: Rubric I20–I25; stroke: Rubric I60–I69, and G45). Diagnoses were ascertained by an outcome adjudication committee (the Cohort Outcome Panel) consisting of an internist, a cardiologist, an endocrinologist, the physician who gathered the data and other invited experts as needed.

Statistical analysis

Sex-separated baseline characteristics were presented as mean (standard deviation) for continuous variables or number (%) for the categorical variables, across glycemic status categories. Sex-specific incidence per 1000 person-years was calculated with 95% confidence intervals (CIs) for each outcome, across glycemic categories.

Cox proportional hazards models were applied separately in men, women and the whole population to assess the associations of glycemic status categories with each outcome of interest. For CHD, stroke and mortality, the event-date equaled the exact date of incidence. However, because for T2D, hypertension and CKD an exact date cannot be attributed to the incidence of disease, the event-date was defined as the mid-point in the time between the follow-up visit when the diagnosis was made for the first time and the most recent visit preceding its diagnosis. Censoring was defined as leaving the residence area, being lost to follow-up or remaining until the end of the study. Follow-up duration was calculated as the time difference between entrance to the study and the event-date or censoring, whichever occurred first. Adjusted hazard ratios (aHRs) for incident outcomes associated with different glycemic categories were estimated in reference to normoglycemia. Initially, models were age-adjusted. Secondary models were adjusted for potential confounders based on the outcome of interest including education, waist-to-hip ratio, BMI, total cholesterol, triglycerides, eGFR, smoking, lipid-lowering medication use, hypertension (except for the hypertension models), prevalent CVD (except for CHD and stroke models), family history of diabetes (only for the T2D models) and family history of CVD (only for CHD and stroke models).

To investigate whether sex modifies the associations between glycemic status categories and outcomes, the interaction terms of glycemic status categories with sex were introduced into the multivariate models. Since significant gender-interactions were observed with incident hypertension, CKD and CHD, the analyses were sex-stratified. Yet, to be comparable with previous studies, all models were also built in the pooled sample, adjusting for sex.

The proportional hazards assumption in the Cox model was proved appropriate by the Schoenfeld residual test and log–log plots. Since this was an exploratory investigation, the significance level was defined at $p < 0.05$ (two sided) for all statistical tests and no adjustments were made for multiple comparisons.[18–20] All statistical analyses were performed using STATA version 12.0 (Stata Corp. LP, College Station, Texas, USA).

Results

Sex-specific baseline characteristics according to glycemic status are shown in Tables 1 and 2, respectively. Compared with men with IFG-WHO, those with IFG-ADA had a better cardiometabolic risk profile and lower frequency of prevalent hypertension and CVD (Table 1). Similarly, among women, those with IFG-ADA had a better cardiometabolic risk profile (except for lower eGFR and higher DBP) and lower prevalence of hypertension and CVD (Table 2).

Subjects were followed up for approximately 12 years (details in Figure 1). Sex-specific age- and multivariate aHRs for each impaired glycemic category in reference to normoglycemia, in association with soft (i.e. T2D, CKD and hypertension) and hard clinical outcomes (i.e. CHD, stroke and mortality), are presented in Tables 3 and 4, respectively. These tables also show the $p_{\text{interaction}}$ between sex and each impaired glycemic category in the multivariate models. Regarding T2D, all definitions of prediabetes were associated with at least 3.9 times increased risk among both genders (all $p_{\text{interaction}} > 0.1$). IFG-ADA for hypertension among men and for CHD among women, IFG-WHO for hypertension among women and IGT for hypertension in both genders remained significant predictors only in age-adjusted models; however, after further adjustments for potential confounders, the risk attenuated between 12% and 20% and reached null.

Focusing on prediabetes in the multivariate models, regarding CKD, IFG-ADA was a marginally significant risk factor among men (aHR 1.28, CI 95% 0.99–1.65, $p = 0.056$), but not women ($P_{\text{interaction}} = 0.008$).

Table 1. Baseline characteristics of participants by different definitions of glycemic status category among men.

Baseline characteristics	ADA fasting glucose clinical categories			WHO fasting glucose clinical categories			ADA and WHO 2-h glucose clinical categories		
	Normoglycemia <5.6 mmol/L $n=2726$	Prediabetes 5.6–6.9 mmol/L $n=585$	Undiagnosed T2D ≥7.0 mmol/L $n=135$	Normoglycemia <6.1 mmol/L $n=3110$	Prediabetes 6.1–6.9 mmol/L $n=201$	Undiagnosed T2D ≥7.0 mmol/L $n=135$	Normoglycemia <7.8 mmol/L $n=2767$	Prediabetes 7.8–11.0 mmol/L $n=431$	Undiagnosed T2D ≥11.0 mmol/L $n=248$
Continuous variables									
Age, years	46.48 (12.81)	51.94 (13.05)	55.25 (11.07)	47.02 (12.92)	54.11 (12.68)	55.25 (11.07)	45.96 (12.55)	54.27 (12.52)	56.43 (12.08)
BMI, kg/m^2	25.87 (3.83)	27.37 (4.02)	27.89 (3.97)	25.99 (3.85)	28.37 (4.06)	27.89 (3.97)	25.84 (3.84)	27.43 (3.97)	28.20 (3.79)
Waist/hip ratio	0.92 (0.06)	0.95 (0.06)	0.98 (0.07)	0.92 (0.06)	0.97 (0.7)	0.98 (0.07)	0.92 (0.06)	0.96 (0.06)	0.98 (0.07)
eGFR, ml/min per 1.73 m^2	72.98 (11.55)	69.22 (12.02)	68.97 (9.66)	72.57 (11.60)	68.42 (12.89)	68.97 (9.66)	73.26 (11.36)	67.66 (12.08)	68.03 (11.45)
Triglycerides, mmol/L	2.03 (1.26)	2.47 (1.89)	2.96 (2.17)	2.06 (1.29)	2.91 (2.41)	2.96 (2.17)	2.02 (1.31)	2.50 (1.71)	2.92 (1.96)
Total cholesterol, mmol/L	5.29 (1.08)	5.55 (1.08)	5.81 (1.11)	5.32 (1.08)	5.64 (1.11)	5.81 (1.11)	5.27 (1.06)	5.63 (1.09)	5.77 (1.16)
HDL-C, mmol/L	0.98 (0.24)	0.97 (0.26)	0.93 (0.21)	0.98 (0.24)	0.95 (0.26)	0.93 (0.21)	0.97 (0.24)	0.98 (0.24)	0.96 (0.27)
Systolic BP, mmHg	119.16 (17.89)	128.39 (20.67)	132.76 (20.39)	119.98 (18.03)	133.38 (24.29)	132.76 (20.39)	118.68 (17.49)	129.78 (19.41)	135.25 (22.96)
Diastolic BP, mmHg	77.52 (10.98)	80.96 (11.83)	81.89 (12.58)	77.81 (11.03)	83.07 (12.91)	81.89 (12.58)	77.34 (10.77)	81.76 (12.06)	82.64 (13.24)
Categorical variables									
Smoking	894 (32.8)	155 (26.5)	35 (25.9)	999 (32.1)	50 (24.9)	35 (25.9)	919 (33.2)	103 (76.1)	62 (25)
Education									
< 6 years	765 (28.1)	230 (39.3)	59 (43.7)	902 (29)	93 (46.3)	59 (43.7)	741 (26.8)	197 (45.7)	116 (46.8)
6–12 years	1447 (53.1)	270 (46.2)	56 (41.5)	1639 (52.7)	78 (38.8)	56 (41.5)	1486 (53.7)	189 (43.9)	98 (39.5)
>12 years	514 (18.9)	85 (14.5)	20 (14.8)	569 (18.3)	30 (14.9)	20 (14.8)	540 (19.5)	45 (10.4)	34 (13.7)
Family history of diabetes	623 (22.9)	180 (30.8)	56 (41.5)	738 (23.7)	65 (32.3)	56 (41.5)	664 (24)	104 (24.1)	91 (36.7)
Family history of CVD	411 (15.1)	509 (87)	115 (85.2)	461 (14.8)	26 (12.9)	20 (14.8)	422 (15.3)	56 (13)	29 (11.7)
Lipid-lowering drug	49 (1.8)	21 (3.6)	2 (1.5)	60 (1.9)	10 (5)	2 (1.5)	52 (1.9)	12 (2.8)	38 (15.3)
Prevalent hypertension	534 (19.6)	215 (36.8)	76 (56.3)	650 (20.9)	99 (49.3)	59 (43.7)	511 (18.5)	173 (40.1)	124 (50)
Prevalent CVD	148 (5.4)	50 (8.5)	14 (10.4)	174 (5.6)	24 (11.9)	14 (10.4)	128 (4.6)	46 (10.7)	38 (15.3)

Data are mean (SD) for continuous and *n* (%) for categorical variables.

ADA: American Diabetes Association; WHO: World Health Organization; T2D: type 2 diabetes mellitus; BMI: body mass index; eGFR: estimated glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; BP: blood pressure; CVD: cardiovascular disease.

Table 2. Baseline characteristics of participants by different definitions of glycemic status category among women.

	ADA fasting glucose clinical categories			WHO fasting glucose clinical categories			ADA and WHO 2-h glucose clinical categories		
Baseline characteristics	Normoglycemia <5.6 mmol/L $n=2726$	Prediabetes 5.6-6.9 mmol/L $n=585$	Undiagnosed T2D ≥7.0 mmol/L $n=135$	Normoglycemia <6.1 mmol/L $n=3110$	Prediabetes 6.1–6.9 mmol/L $n=201$	Undiagnosed T2D ≥7.0 mmol/L $n=135$	Normoglycemia <7.8 mmol/L $n=2767$	Prediabetes 7.8–11.0 mmol/L $n=431$	Undiagnosed T2D ≥11.0 mmol/L $n=248$
Continuous variables									
Age, years	44.47 (11.15)	50.33 (10.89)	54.11 (10.18)	45.13 (11.29)	50.57 (10.64)	54.10 (10.18)	44.33 (11.09)	49.66 (11.32)	52.64 (10.30)
BMI, kg/m^2	28.04 (4.62)	30.41 (4.95)	30.83 (4.36)	28.29 (4.71)	30.70 (4.96)	30.83 (4.36)	28.07 (4.65)	29.91 (4.88)	30.41 (4.56)
Waist/hip ratio	0.85 (0.07)	0.88 (0.07)	0.93 (0.07)	0.85 (0.08)	0.89 (0.07)	0.93 (0.07)	0.84 (0.08)	0.88 (0.07)	0.91 (0.07)
eGFR, ml/min per 1.73 m^2	67.58 (10.61)	64.15 (10.02)	62.56 (10.21)	67.14 (10.64)	64.79 (9.51)	62.56 (10.21)	67.55 (10.58)	65.01 (10.46)	63.23 (9.91)
Triglycerides, mmol/L	1.77 (1.00)	2.34 (1.37)	2.77 (1.41)	1.83 (1.07)	2.39 (1.29)	2.77 (1.41)	1.73 (0.97)	2.29 (1.28)	2.83 (1.43)
Total cholesterol, mmol/L	5.51 (1.11)	5.96 (1.20)	6.38 (1.43)	5.55 (1.18)	6.03 (1.22)	6.38 (1.43)	5.47 (1.16)	5.99 (1.21)	6.23 (1.35)
HDL-C, mmol/L	1.16 (0.28)	1.12 (0.27)	1.12 (0.28)	1.15 (0.28)	1.11 (0.27)	1.12 (0.28)	1.16 (0.28)	1.13 (0.29)	1.10 (0.28)
Systolic BP, mmHg	117.72 (18.46)	128.84 (20.42)	136.08 (23.37)	118.97 (18.99)	129.25 (20.84)	136.08 (23.37)	117.11 (18.04)	128.31 (20.65)	135.29 (22.00)
Diastolic BP, mmHg	77.58 (10.57)	82.10 (10.39)	83.92 (11.92)	78.11 (10.64)	81.91 (10.51)	83.92 (11.92)	77.30 (10.38)	82.15 (10.89)	83.88 (11.16)
Categorical variables									
Smoking	162 (5)	23 (3.5)	5 (3.2)	182 (5)	3 (1.2)	5 (3.2)	160 (5.2)	19 (3)	11 (3.6)
Education									
<6 years	1356 (42)	390 (59)	122 (77.2)	1595 (43.7)	151 (62.1)	122 (77.2)	1284 (41.4)	375 (58.4)	209 (68.5)
6–12 years	1575 (48.7)	240 (36.3)	34 (21.5)	1732 (47.5)	83 (34.2)	34 (21.5)	1526 (49.2)	232 (36.1)	91 (29.8)
>12 years	301 (9.3)	31 (4.7)	2 (1.3)	323 (8.8)	9 (3.7)	2 (1.3)	294 (9.5)	35 (5.5)	5 (1.6)
Family history of diabetes	885 (27.4)	234 (35.4)	76 (48.1)	1007 (27.6)	112 (46.1)	76 (481)	839 (27)	221 (34.4)	135 (44.3)
Family history of CVD	556 (17.2)	137 (20.7)	32 (20.3)	651 (17.8)	42 (17.3)	32 (20.3)	532 (17.1)	124 (19.3)	69 (22.6)
Lipid lowering drug	103 (3.2)	41 (6.2)	7 (4.4)	132 (3.6)	12 (4.9)	7 (4.4)	87 (2.8)	46 (7.2)	18 (5.9)
Prevalent hypertension	681 (21.1)	275 (42.1)	82 (51.9)	849 (23.3)	110 (45.3)	82 (51.9)	616 (19.8)	267 (41.6)	158 (51.8)
Prevalent CVD	102 (3.2)	40 (6.1)	9 (5.7)	125 (3.4)	17 (7)	9 (5.7)	94 (3)	38 (5.9)	19 (6.2)

Data are mean (SD) for continuous and *n* (%) for categorical variables.

ADA: American Diabetes Association; WHO: World Health Organization; T2D: type 2 diabetes mellitus; BMI: body mass index; eGFR: estimated glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; BP: blood pressure; CVD: cardiovascular disease.

Table 3. Age and multivariate adjusted hazard ratio for incident soft clinical outcomes across categories of glycemic status in men and women.

			Incident diabetes[a] HR (95% CI)		Chronic kidney disease[b] HR (95% CI)		Hypertension HR (95% CI)	
			Men $n=2533$, $E=421$	Women $n=3082$, $E=535$	Men $n=2723$, $E=382$	Women $n=2763$, $E=758$	Men $n=2422$, $E=816$	Women $n=2773$, $E=905$
ADA fasting glucose definition	< 5.6 mmol/L		1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	5.6–6.9 mmol/L	Age	5.03 (4.11–6.11)*	5.35 (4.47–6.39)*	1.33 (1.04–1.71)*	1.03 (0.84–1.26)	1.24 (1.04–1.49)*	1.52 (1.28–1.82)*
		Multivariate	4.15 (3.39–5.06)*	4.31 (3.59–5.17)*	1.28 (0.99–1.65)**	1.01 (0.82–1.23)	1.09 (0.91–1.32)	1.24 (1.04–1.48)*
	≥7.0 mmol/L	Age	–	–	2.15 (1.46–3.17)*	1.01 (0.71–1.41)	1.47 (1.03–2.10)*	1.88 (1.37–2.58)*
		Multivariate	–	–	1.93 (1.29–2.87)*	1.00 (0.69–1.44)	1.18 (0.82–1.71)	1.43 (1.04–1.97)*
			$p_{interaction}$ 0.97		$p_{interaction}$ 0.008		$p_{interaction}$ 0.068	
WHO fasting glucose definition	< 6.1 mmol/L		1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	6.1–6.9 mmol/L	Age	6.16 (4.74–8.01)*	7.11 (5.66–8.92)*	1.08 (0.73–1.62)	0.87 (0.63–1.18)	1.26 (0.92–1.74)	1.36 (1.03–1.79)*
		Multivariate	4.41 (3.32–5.82)*	3.91 (3.26–4.68)*	1.01 (0.66–1.52)	0.86 (0.63–1.18)	1.01 (0.73–1.40)	1.09 (0.83–1.44)
	≥7.0 mmol/L	Age	–	–	1.90 (1.29–2.78)*	0.99 (0.69–1.41)	1.43 (1.01–2.04)*	1.77 (1.29–2.42)*
		Multivariate	–	–	1.80 (1.21–2.67)*	0.98 (0.68–1.41)	1.16 (0.82–1.67)	1.36 (0.99–1.88)
			$p_{interaction}$ 0.10		$p_{interaction}$ 0.027*		$p_{interaction}$ 0.177	
ADA/WHO 2-h glucose definition	< 7.8 mmol/L		1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	7.8–11.0 mmol/L	Age	5.37 (4.37–6.60)*	4.81 (4.03–5.72)*	1.16 (0.87–1.53)	0.92 (0.76–1.32)	1.23 (1.01–1.52)*	1.30 (1.09–1.56)*
		Multivariate	4.08 (3.30–5.06)*	5.72 (4.53–7.22)*	1.11 (0.83–1.50)	0.83 (0.67–1.02)	1.01 (0.81–1.23)	1.10 (0.92–1.32)
	≥ 11.0 mmol/L	Age	–	–	1.83 (1.34–2.51)*	1.01 (0.77–1.31)	1.23 (0.92–1.65)	1.93 (1.51–2.44)*
		Multivariate	–	–	1.85 (1.32–2.55)*	0.95 (0.71–1.25)	0.96 (0.71–1.28)	1.42 (1.11–1.82)*
			$p_{interaction}$ 0.74		$p_{interaction}$ 0.003*		$p_{interaction}$ 0.009*	

Tehran Lipid and Glucose Study (1999–2015). Cox proportional hazard models were applied to calculate hazard ratios and 95% confidence intervals. All multivariate models were adjusted for: age, body mass index, education level, waist/hip ratio, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, smoking, lipid-lowering drug, prevalent cardiovascular disease; additional adjustments were [a]hypertension, family history of diabetes; [b]hypertension. $p_{interaction}$ between sex and glycemic status category in the multivariate model is presented for each outcome.
*$p < 0.05$.
**$p = 0.05$.
E: Number of events; HR: hazard ratio; CI: confidence interval; Ref.: reference; ADA: American Diabetes Association; WHO: World Health Organization.

Table 4. Age and multivariate adjusted hazard ratio for incident hard clinical outcomes across categories of glycemic status in men and women.

			Coronary heart disease[a] HR (95% CI)		Stroke[a] HR (95% CI)		All-cause mortality[b] HR (95% CI)	
			Men $n=3236$, $E=371$	Women $n=3902$, $E=215$	Men $n=3236$, $E=70$	Women $n=3902$, $E=54$	Men $n=3446$, $E=262$	Women $n=4051$, $E=133$
ADA fasting glucose definition	<5.6 mmol/L		1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	5.6–6.9 mmol/L	Age	0.95 (0.73–1.25)	1.55 (1.14–2.12)*	1.58 (0.93–2.70)	1.46 (0.78–2.70)	1.01 (0.75–1.37)	1.15 (0.77–1.72)
		Multivariate	0.83 (0.62–1.08)	1.27 (0.93–1.75)	1.36 (0.78–2.37)	1.30 (0.69–2.44)	1.00 (0.73–1.35)	1.09 (0.72–1.66)
	≥7.0 mmol/L	Age	2.25 (1.57–3.22)*	2.23 (1.43–3.47)*	2.42 (1.09–5.39)*	2.05 (0.90–4.67)	2.40 (1.62–3.55)*	1.47 (0.82–2.64)
		Multivariate	1.67 (1.15–2.43)*	1.45 (0.92–2.31)	2.40 (1.03–5.58)*	1.35 (0.56–3.22)	2.67 (1.77–4.02)*	1.43 (0.78–2.64)
			$p_{interaction}$ 0.13		$p_{interaction}$ 0.60		$p_{interaction}$ 0.476	
WHO fasting glucose definition	<6.1 mmol/L		1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	6.1–6.9 mmol/L	Age	1.14 (0.77–1.70)	1.52 (0.98–2.38)	2.43 (1.26–4.67)*	0.95 (0.34–2.66)	0.84 (0.54–1.34)	0.93 (0.49–1.79)
		Multivariate	0.93 (0.62–1.41)	1.24 (0.79–1.95)	2.15 (1.08–4.27)*	0.84 (0.29–2.39)	0.78 (0.48–1.26)	0.86 (0.45–1.67)
	≥7.0 mmol/L	Age	2.29 (1.61–3.27)*	2.05 (1.33–3.17)*	2.38 (1.08–5.25)*	1.83 (0.82–4.09)	2.36 (1.60–3.47)*	1.31 (0.79–2.51)
		Multivariate	1.75 (1.21–2.54)*	1.37 (0.87–2.16)	2.48 (1.08–5.70)*	1.21 (0.52–2.82)	2.54 (1.69–3.81)*	1.37 (0.75–2.48)
			$p_{interaction}$ 0.94		$p_{interaction}$ 0.21		$p_{interaction}$ 0.262	
ADA/WHO 2–h glucose definition	<7.8 mmol/L		1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8–11.0 mmol/L	Age	1.18 (0.89–1.56)	1.95 (1.43–2.66)*	1.54 (0.86–2.76)	0.73 (0.34–1.52)	1.19 (0.86–1.64)	1.29 (0.86–1.94)
		Multivariate	0.98 (0.73–1.31)	1.57 (1.14–2.16)*	1.31 (0.72–2.38)	0.61 (0.28–1.27)	1.18 (0.88–1.64)	1.26 (0.83–1.90)
	≥11.0 mmol/L	Age	1.77 (1.30–2.43)*	2.28 (1.57–3.32)*	2.16 (1.13–4.12)*	1.53 (0.76–3.11)	1.79 (1.29–2.48)*	1.43 (0.88–2.35)
		Multivariate	1.28 (0.93–1.78)	1.60 (1.08–2.38)*	1.82 (0.91–3.66)	1.00 (0.46–2.15)	1.79 (1.26–2.57)*	1.33 (0.78–2.24)
			$p_{interaction}$ 0.057**		$p_{interaction}$ 0.24		$p_{interaction}$ 0.913	

Tehran Lipid and Glucose Study (1999–2015). Cox proportional hazard models were applied to calculate hazard ratios and 95% confidence intervals. All multivariate models were adjusted for: age, body mass index, education level, waist/hip ratio, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, smoking, lipid-lowering drug, and hypertension; additional adjustments were [a]family history of cardiovascular disease; [b]prevalent cardiovascular disease.

$p_{interaction}$ for sex and glycemic status category in the multivariate model is presented for each outcome.

*$p < 0.05$

**$p = 0.05$

E: Number of events; HR: hazard ratio; CI: confidence interval; Ref.: reference; ADA: American Diabetes Association; WHO: World Health Organization

By contrast, IFG-ADA increased the risk of hypertension only among women (aHR 1.24, CI 95% 1.04–1.48; $p_{interaction} = 0.06$). IFG-WHO and IGT were not associated with CKD or hypertension in either gender. Regarding CHD, IGT was associated with increased risk (aHR 1.57, CI 95% 1.14–2.16); yet no associations were found in men ($p_{interaction} = 0.05$). IFG was not associated with CHD after multivariate adjustment in any gender. Regarding stroke, only men with IFG-WHO showed increased risk (aHR 2.15, CI 95% 1.08–4.27; $p_{interaction} = 0.21$). IFG-ADA and IGT were not associated with stroke in either gender. None of the definitions of prediabetes were associated with mortality (all p-values > 0.2) and no gender-difference was noted (all $p_{interaction} > 0.2$).

Supplementary Tables 2 and 3 show the incidence rates per 1000 person-years and Supplementary Table 4 presents the sex-adjusted models for all clinical outcomes, across the glycemic categories.

Discussion

In this population-based study from the Middle East, we highlight sex-specific associations between prediabetes definitions and major clinical outcomes over a decade long follow-up. Our results indicate the associations of IFG-ADA with CKD and IFG-WHO with stroke, only among men, and the associations of IFG-ADA with incident hypertension and IGT with CHD, only among women. Using any definition of prediabetes in both genders increased the risk of incident T2D to more than four-fold.

The progression rates of IFG-ADA, IFG-WHO and IGT to overt T2D either among men or among women in our study (Supplementary Tables 2 and 3) were generally higher than the corresponding values in the whole population from a large meta-analysis which documented incidence rates of 35.5, 47.4 and 45.5 per 1000 person-years, respectively.[21] As expected, all definitions of prediabetes were associated with incident T2D[2], and confirming a previous study from China, risk of T2D was similar between men and women.[22]

Regarding CKD, to the best of our knowledge, this is the first study to find a significant association with IFG-ADA, which was only present among men. A recent meta-analysis reported 11% increase in the risk of CKD with IFG-WHO,[4] yet with marked heterogeneity and no sex-separated analysis among studies. In agreement with our sex-adjusted results (Supplementary Table 4), the only study including both genders and adequate adjustments for IFG-WHO and the two studies on IFG-ADA found no significant association with CKD in the whole population from other ethnicities.[4] The sex-difference pointed out by our findings is in line with previous observations in the general population, indicating an association between male gender with adverse renal outcomes.[23] This might be explained by the protective effect of female sex hormones;[24] however, this effect seems to disappear in diabetic women, probably because of hormone imbalance in a hyperglycemic environment,[25] as diabetic men and women have shown similar risk of CKD.[24] Our previous results from Tehranian adults indicated a dramatic increased risk of CKD among women with known diabetes, whereas undiagnosed diabetes only increased the risk among men.[13] Considering that patients with known diabetes have probably been under the effect of hyperglycemia for a longer period, these observations could indicate the potential importance of duration of hyperglycemia in its harmful renal effects in women. To illuminate this matter, further studies are desired to consider the impact of duration of prediabetes in its association with incident CKD in each gender. Regarding the association of IGT with CKD, studies are too scarce to be conclusive.[4,26] In this study, we failed to find any association between IGT and CKD, as defined by eGFR decline. Previously a higher prevalence of albuminuria, an early marker of CKD, has been shown in IGT compared with normoglycemia.[27] Moreover, IGT, but not IFG, has been associated with glomerular hyperfiltration.[28] Therefore, investigating the association of IGT with albuminuria is recommended for future studies.

For incident hypertension, we showed 24% increased risk among women with IFG-ADA; yet no definitions of IFG were associated with hypertension among men. Insulin resistance could lead to hypertension through several mechanisms, including sympathetic stimulation and renin–angiotensin–aldosterone system activation.[15] The observed sex-difference in the association of IFG with hypertension is in line with our previous study where insulin resistance parameters were only associated with incident hypertension among women.[10] Previously, a Korean cohort[6] and the Multi-Ethnic Study of Atherosclerosis[5] failed to find any independent associations between IFG-ADA with incident hypertension. Yet, none of these studies documented sex-separated analyses. Contrasting our findings among TLGS men, the Osaka Health Survey on Japanese men indicated a positive association between IFG-WHO and hypertension.[29] However, the study lacked adjustment for central adiposity, an important confounding factor in the association between insulin resistance and hypertension,[15] especially among men.[10] To our knowledge, this is the first evidence of a sex-specific association between IFG-ADA with hypertension, independent of general or central adiposity. Our findings are in line with previous studies suggesting a dominant link between insulin resistance, arterial stiffness and hypertension among women, compared with

men, probably under the effect of sex hormones.[9,10,30] Yet, further studies are required to confirm the sex-difference and underlying mechanisms. The IGT phenotype, in the current study, as well as in the study by Lee et al., increased the risk of hypertension more than 20%, which did not remain significant after multivariate adjustments.[6] Considering that both studies have adjusted for similar confounders, including anthropometric measures and lipid profile, this suggests that IGT may not have a true effect on incident hypertension independent of other cardiometabolic risk factors.

Regarding cardiovascular events, many studies have considered composite CVD as the outcome.[7] Yet, there may be different associations between prediabetes with CHD and stroke masking each other when combined as composite CVD.[31] Recently, in a large meta-analysis, Huang et al.[7] showed that IFG-ADA, IFG-WHO and IGT all increased the risk of CHD (by relative risks of 1.10, 1.18 and 1.20, respectively) and stroke (by relative risks of 1.06, 1.17 and 1.20, respectively). It is noticeable that despite the high risk of CVD and its risk factors in the Middle East,[14] eligible studies from this region were scarce. Moreover, only few studies presented sex-separated analyses. In our study, despite the low number of events, IFG-WHO increased the risk of stroke among men and IGT increased CHD risk among women, both with hazard ratios comparable to undiagnosed diabetes. Regarding CHD, our results are in line with the previous studies from Europe and Asia, indicating a stronger link with IGT compared with IFG.[32,33] However, in contrast to our findings on sex-difference, the DECODE study, recruiting data from 10 European prospective cohorts, demonstrated a stronger association between IGT and CHD-related mortality among men than among women.[32] Yet, our results follow the previous research indicating a higher impact of hyperglycemia on cardiac structure among non-diabetic women[34] and a higher incidence of CHD among diabetic women compared with their male counterparts.[35] Regarding stroke, our findings build on previous studies conducted among non-diabetic men from Korea and the USA, which demonstrated a markedly increased risk of stroke with rising FPG above the WHO cutoff,[31,36] and confirm the results of Kim et al., indicating that the association exists only among men and not among women.[37] However, studies from Japan failed to find any association between IFG-ADA/-WHO with ischemic stroke, for either gender,[38,39] despite increased risk of stroke-mortality in men and CHD-mortality in women with known diabetes.[40] Regarding IGT, similar to our study population, no association was found with stroke among Japanese adults.[39] Overall, the disparities between studies on stroke could be due to ethnicity, different definitions of outcome (e.g. all stroke *vs.* ischemic stroke) or the variety in covariate adjustments.

Last, in our population, none of the prediabetes definitions were significantly associated with all-cause mortality and no sex-difference was found. Our findings were partly in line with the recent meta-analysis by Huang et al.,[7] who reported no sex-difference in the association of prediabetes definitions with mortality; however, unlike our results, they concluded significant increased risk of mortality by 13% with IFG-ADA and -WHO and by 32% with IGT. Generally, studies on the association of IGT with mortality have been more consistent and documented stronger associations than studies on IFG.[7] Similarly, in our population, compared with IFG, IGT showed stronger associations with mortality with aHRs of 1.18 (0.88–1.64) among men and 1.26 (0.83–1.90) among women; yet our study power to detect the significance of these associations was around 25%.

As it has been argued for the sex-differences in complications of insulin resistance and overt T2D, it is not yet clear whether these differences are solely due to intrinsic and biological mechanisms or whether environmental factors such as risk factor control and lifestyle also play a role.[11] Further studies are essential to clarify these gender-differences among different populations and investigate the underlying mechanisms. Eventually, if confirmed, these results could suggest the need for sex-specific definitions of prediabetes and, subsequently, sex-specific approaches to its management.

The most important strengths of this study are the prospective population-based design with long-term follow-up, reasonable size of population, providing data on both FPG and 2h-PCPG levels and for both sexes, accurate data measurements at baseline and continuous surveillance for major outcomes, which were ascertained by an adjudication committee. Moreover, this is among the first studies to highlight sex-differences in the association of prediabetes with major clinical outcomes and the first, to our knowledge, to find sex-specific associations between IFG-ADA and CKD and hypertension.

Limitations

Most importantly, in this study we did not account for the changes in prediabetes status during follow-up. Hence, like many relevant studies,[31,33,39] we were unable to tell whether the observed risks were due to prediabetes per se or its progression to diabetes. As this was a hypothesis driven exploratory study, adjustments for multiple testing were not performed to avoid obscuring potentially true associations.[18,20] In fact, we intended to limit type II error (incorrect confirmation of the null hypothesis), which would increase with

multiple testing, in exchange for a decrease in type I error. However, our findings need to be proved by further confirmatory studies before being used in decision-making.[19] Although we adjusted for a wide variety of covariates, as appropriate for each outcome, residual confounders such as physical activity, nutritional status and socio-economic status may alter the results. Regarding our clinical endpoints, as with many epidemiologic studies,[4] CKD was diagnosed based on a single measurement of serum creatinine and data on albuminuria were not available. Moreover, eGFR was estimated by the CKD-EPI equation, which has not been validated in a local population. Due to limited statistical power, we could not separate stroke subtypes in our analyses. Previously, Sung et al.[31] observed different associations between IFG-WHO and hemorrhagic and ischemic stroke among men, suggesting that including hemorrhagic stroke may mask the risk of IFG for ischemic stroke. Yet, in our study, only 26 cases of stroke were hemorrhagic. Last, due to the nature of observational studies, no causality can be determined between prediabetes and clinical outcomes based solely on this study.

Conclusions

In conclusion, this study sheds light on gender-differences in the clinical outcomes of prediabetes. Our results from a region with a high burden of cardiometabolic risk factors indicate that IFG-ADA can identify high-risk men for CKD and high-risk women for hypertension. Moreover, the risk of stroke in men with IFG-WHO and CHD in women with IGT is nearly as high as undiagnosed diabetes. Considering gender-differences in approaching prediabetes could improve individualized management of this condition.

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Author contribution

FH, DP, NR and FA contributed to the conception or design of the study. DP, FH, SA contributed to the acquisition, analysis or interpretation of data. DP, NR and SA drafted the manuscript. FH, FA, DP critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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