ORIGINAL RESEARCH

Different Combinations of Glucose Tolerance and Blood Pressure Status and Incident Diabetes, Hypertension, and Chronic Kidney Disease

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***Background*—**The impact of different combinations of glucose tolerance and blood pressure status on the development of type 2 diabetes mellitus (T2DM), hypertension (HTN), and chronic kidney disease (CKD) still needs to be investigated.

***Methods and Results*—**A total of 12 808 Iranian adults aged ≥20 years were included in 3 separate analyses to investigate incidence of T2DM, HTN, and CKD. Multivariate Cox proportional hazard models were used to calculate hazard ratios (95% CI). During a median follow-up of >10 years, the overall incidence rate for T2DM, HTN, and CKD was 12.2, 29.8, and 24.8 per 1000 person-years. For incident T2DM, considering normal glucose tolerance/normal blood pressure as reference, prediabetes (PreDM)/HTN had the highest risk (hazard ratio: 7.22 [5.71–9.12]) while PreDM/normal blood pressure also showed a significant risk (5.58 [4.41–7.05]). Furthermore, risk of PreDM/HTN was higher than PreDM/normal blood pressure ($P<0.05$). For incident HTN, normal glucose tolerance/prehypertension was a strong predictor (3.28 [2.91–3.69]); however, addition of PreDM or T2DM did not increase the risk. For incident CKD, every category that included HTN and/or T2DM showed significant risk; this risk was marginally significant for the PreDM/HTN group (1.19 [0.98–1.43], $P=0.06$). In addition, PreDM/ normal blood pressure was a marginally significant risk factor for incident HTN while normal glucose tolerance/prehypertension was a significant predictor of T2DM.

***Conclusions*—**Presence of HTN was associated with increased risk of T2DM among the PreDM population; however, dysglycemia did not increase the risk of HTN among individuals with prehypertension. For incident CKD, intensive management of HTN and T2DM, rather than their predisease states, should be considered. **(*J Am Heart Assoc*. 2016;5:e003917 doi: 10.1161/JAHA.116.003917)**

Key Words: blood pressure • chronic kidney disease • diabetes • glucose tolerance • hypertension • prediabetes • prehypertension

Hypertension (HTN) is the main risk factor leading to cardiovascular events.[1] In addition, type 2 diabetes mellitus (T2DM) and different phenotypes of glucose intolerance are rising globally, resulting in a higher incidence and burden of their complications.[2] Several studies have shown that the combination of T2DM and HTN results in a much higher risk for further complications, and also these 2 diseases are independent risk factors for developing each other.[3–5] Individuals with abnormal glucose levels have a higher risk for developing abnormal blood pressure and vice versa.[3,4,6] Moreover, prediabetes (PreDM) as a high-risk state for T2DM is an independent risk factor for progression to HTN, while it is also responsible for a higher risk of mortality.[7–9] On the other hand, prehypertension (PreHTN), as proposed by the Joint National Committee 7, is a risk factor for development of type T2DM as well as HTN.[10–12] Recently, we reported a high incidence of PreDM and PreHTN among the Iranian population.[13,14] Despite this, we did not confirm any impact of fasting plasma glucose (FPG) and 2-hour postchallenge plasma glucose (2 h-PCPG) on incident HTN and we did not find any relations between systolic and diastolic blood pressure (SBP and DBP) with incident T2DM among the adult population of Tehran.[15,16]

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Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/5/8/e003917/DC1/embed/inline-supplementary-material-1.pdf

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One of the most important complications of both T2DM and HTN is loss of renal function and eventually chronic kidney disease (CKD), which has a high incidence among Iranian population.[17] Also, both PreHTN and PreDM have been suggested as risk factors associated with decreased glomerular filtration rate (GFR).[18,19] In the current study, we aim to investigate the impact of different combinations of glycemic status phenotypes (ie, normoglycemia, PreDM, and T2DM) and blood pressure status (ie, normotension, PreHTN, and HTN) on incident T2DM, HTN, and CKD in a cohort of Iranian adults during more than a decade of follow-up.

Methods

Study Design and Sample

Tehran Lipid and Glucose Study (TLGS) is a prospective population-based study being performed on a representative sample of the population of Tehran, aimed at determining the prevalence and incidence of noncommunicable diseases and their risk factors. To date, it has been conducted in 5 phases (3-year intervals from 1999 to 2015) on 18 432 participants aged ≥3 years from district 13 of Tehran consisting of 15 005 first-phase (1999–2002) and 3427 second-phase recruitments (2002–2005). A detailed description of the TLGS has been reported elsewhere.[20] For the current study, after exclusion of 5624 subjects aged <20 years, 12 808 participants aged ≥20 years who were recruited from the first and second phase of TLGS were selected.

Study Population

Three separate lines of exclusions were carried out for T2DM, HTN, and CKD as the outcomes (Figure). First, for the analysis of incident T2DM, exclusions included 1376 individuals with prevalent T2DM or missing data of glucose tolerance variables (n=1237) along with 1964 individuals who did not attend any follow-ups, resulting in a total number of 8231 participants. Secondly, for the analysis of incident HTN, from a total of 12 808, exclusions included 2660 individuals with prevalent HTN or missing data of blood pressure at baseline (n=917) along with 1862 who did not attend any follow-ups, resulting in a total number of 7369. Finally, for incident CKD, exclusions included 1784 cases of prevalent CKD plus 1009 with missing data of serum creatinine and 1956 individuals who had no follow-up data, which left a total number of 8059 participants for the analysis. The overall response rate of TLGS participants for all outcomes was about 72% (Figure). Informed written consent was obtained from all participants and the Ethical Committee of Research Institute for Endocrine Sciences approved this study.

Clinical and Laboratory Measurements

A trained interviewer collected information including demographic data, drug history, past medical history of cardiovascular disease, T2DM, and smoking status using a standard questionnaire. Details of the anthropometric measurements including weight, height, and waist circumference are reported elsewhere.[20] Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Waist to height ratio was calculated as waist circumference divided by height (cm). After a 15-minute rest in the sitting position, 2 measurements of SBP and DBP were measured by trained personnel, on the right arm, using a standardized mercury sphygmomanometer (calibrated by the Iranian Institute of Standards and Industrial Researches); the mean of the 2 measurements was considered as the participant's blood pressure.

A blood sample was taken between 7:00 and 9:00 AM from all study participants, after 12 to 14 hours of overnight fast. All blood analyses were carried out at the TLGS research laboratory on the day of blood sample collection. For oral glucose tolerance test, 82.5 g glucose monohydrate solution (equivalent to 75 g anhydrous glucose) was administered orally to subjects not on glucose-lowering drugs, and a blood sample was taken 2 hours later. Details of laboratory measurements including FPG, 2 h-PCPG, triglycerides, high-density lipoprotein cholesterol, and serum creatinine are reported elsewhere.[20]

Definition of Terms

Participants were classified as having T2DM at baseline or during follow-up if they met at least 1 of the following criteria: FPG ≥7 mmol/L, 2 h-PCPG ≥11.1 mmol/L or taking antidiabetic medications. Moreover, PreDM was defined as having a 5.55 mmol/L≤FPG<7 mmol/L and/or a 7.77 mmol/L ≤2 h-PCPG <11.1 mmol/L, without using glucose-lowering drugs; those with FPG <5.55 mmol/L and 2 h-PCPG <7.77 mmol/L were considered as normal glucose tolerant (NGT) according to the definition of the American Diabetes Association.[21] HTN at baseline and follow-ups was defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg, or taking antihypertensive medication(s). PreHTN at baseline was defined as the SBP ≥120 and <140 mm Hg and DBP ≥80 and <90 mm Hg and normal blood pressure (NBP) was defined as SBP <120 mm Hg and DBP <80 mm Hg without any medication use.[12] According to the Kidney Disease Outcome Quality Initiative guidelines, CKD is defined as either kidney damage or estimated GFR (eGFR) <60 mL/min per 1.73 m^2 for >3 months.[22] For this study, eGFR was estimated using the abbreviated prediction equation, provided by the CKD-EPI formula as follows:

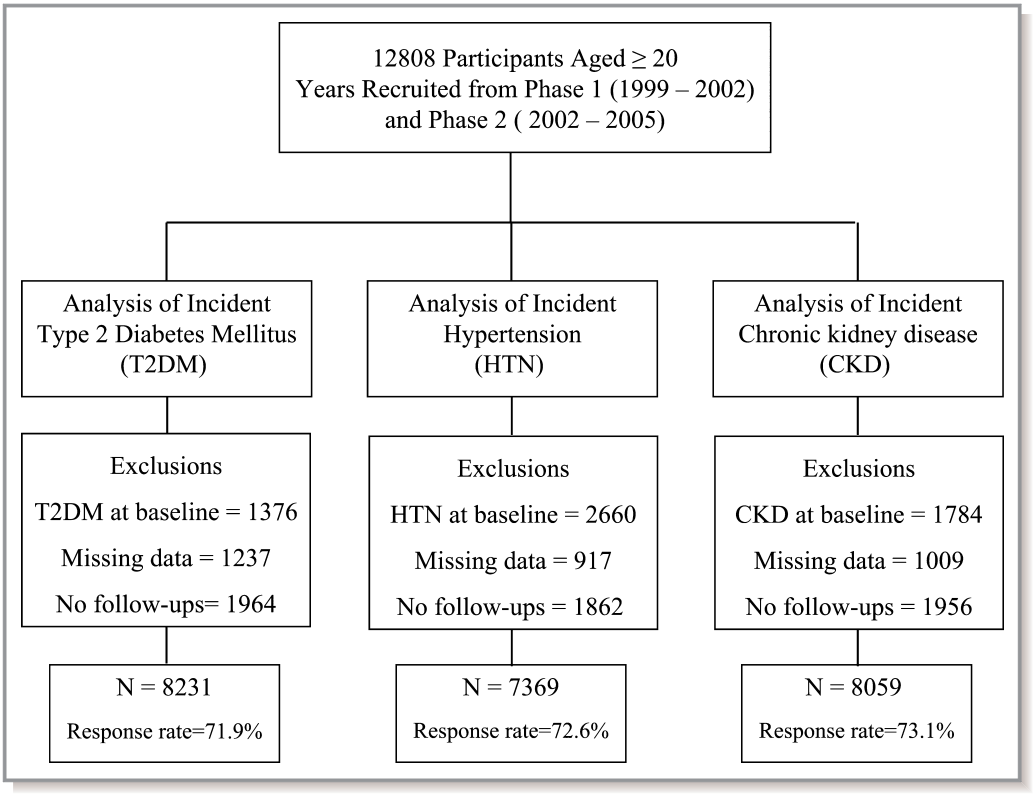

Figure. Flowchart of the study population, Tehran Lipid and Glucose Study, 1999–2015.

$$\text{eGFR} = 141 \times \min(\text{serum creatinine}/\kappa, 1)^{\alpha} \times \max(\text{serum creatinine}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ [if female]}$$

In this equation, eGFR is expressed as mL/min per 1.73 m^2, serum creatinine is expressed as mg/dL, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of serum creatinine/κ or 1 and max indicates the maximum of serum creatinine/κ or 1.[23] Family history of premature cardiovascular disease was defined as a positive history of myocardial infarction or stroke or sudden cardiac death in a male first-degree relative <55 years or female first-degree relative <65. Education was classified into 3 groups: 0 to 5, 6 to 12, and >12 years of education. Physically active participants were identified as those who were participating in a vigorous physical activity at least 3 days per week or achieving a minimum of at least 600 metabolic equivalent task–minutes per week.

Statistical Analysis

Baseline characteristics of participants are shown as mean (SD) or frequency (%) as appropriate. Participants were categorized into 6 groups for the analysis of incident T2DM and incident HTN and into 9 groups for the analysis of incident CKD as shown below:

For incident T2DM: NGT/NBP (as reference), PreDM/NBP, NGT/PreHTN, PreDM/PreHTN, PreDM/HTN and NGT/HTN.

For incident HTN: NGT/NBP (as reference), PreDM/NBP, NGT/PreHTN, PreDM/PreHTN, T2DM/PreHTN and T2DM/NBP.

For incident CKD: NGT/NBP (as reference), PreDM/NBP, NGT/PreHTN, PreDM/PreHTN, T2DM/NBP, T2DM/PreHTN, NGT/HTN, PreDM/HTN and T2DM/HTN.

Cox proportional hazard models were used to evaluate the relations of these categories with the normal group as the reference for incident T2DM, HTN, and CKD. The event date for incident cases was described as the mid-time between the date of follow-up visit at which the disease was detected for the first time, and the most recent follow-up visit preceding the diagnosis; the follow-up time was drawn from the difference between the calculated mid-time date and the date at which the subjects entered the study. For the censored participants, survival time was calculated as the interval between the first and the last observation dates. In addition to an age and sex adjusted model, a multivariable model using well-known risk factors of T2DM, HTN, and CKD was developed. The adjustments for all 3 outcomes were age, sex, BMI (kg/m^2), waist to height ratio, triglycerides/high-density lipoprotein cholesterol ratio, smoking status (current

smokers, past smokers, and nonsmokers as reference), and physical activity. Additionally, family history of T2DM for incident T2DM and family history of premature cardiovascular disease for incident HTN were adjusted for.[15–17] The proportional hazard assumption of the multivariable Cox model was assessed using Schoenfeld's global test of residuals.

Sensitivity Analysis

First, a sensitivity analysis was performed to compare the hazard ratios of the multivariable model for incident T2DM and HTN using PreDM/NBP and NGT/PreHTN as reference, respectively, in place of NGT/NBP. Secondly, to address the issue of selection bias regarding the lost to follow-up participants, another sensitivity analysis was performed. Initially, for the participants who were excluded from the study due to missing data at baseline, Little's Missing Completely at Random Test was used to check whether or not the missing data follow a completely random pattern.[24] The test resulted in a significant *P* value at $P<0.001$. Thus, the null hypothesis (ie, data being Missing Completely at Random in this case) was rejected and there exists a pattern in the missing data.[24] Then, multiple imputation was used for imputation of baseline missing data.[25,26] The number of imputations was decided based on a simple rule of thumb (ie, at least 1 imputation per percent of incomplete cases).[26,27] Since ≈17% of cases were incomplete, the number of imputations was set to 20. After imputation of baseline missing data, 20 complete data sets, each containing data of 12 808 TLGS participants (aged ≥20 years), became available for analysis for each outcome. The next step was to exclude baseline cases of T2DM, HTN, or CKD in all imputed files. Then, lost to follow-up cases were identified in each file. To take into account the selection bias for lost to follow-up cases, propensity scores—the estimated probability that a participant could have been followed in the study—were computed using maximum likelihood logistic regression analysis in the imputed files.[28] For this reason, the entire baseline measures including age, sex, FPG, 2 h-PCPG, triglycerides/high-density lipoprotein cholesterol, SBP, DBP, BMI, waist to height ratio, eGFR, family history of diabetes, family history of premature CVD, education level, and smoking status were included in a logistic model as exposures with participation in the follow-up as the outcome. Then, the probability of participation in follow-up (propensity score) was computed for all participants in each file. Next, the calculated propensity scores were inversed and were added as sampling weight to the Cox regression analysis for each outcome (inverse probability weighting) in each imputed file.[28] Finally, for each outcome, 20 results from Cox regression analysis in the imputed files (hazard ratios [HRs] and 95% CIs) were pooled using the standard rules of Little and Rubin.[29,30] All analyses were performed using SPSS for Windows version 21, STATA version 12 SE (Stata Corp LP, College Station, TX) and R version 3.3.1, with a 2-tailed $P<0.05$ considered significant.

Results

Baseline characteristics of study participants (for incident T2DM) according to their baseline status of glucose tolerance and blood pressure are shown in Table 1. The mean (SD) age of participants was 40.9 (13.6) and mean BMI was 26.6 (4.59) kg/m^2 with 56% of participants being female. Between categories, age, BMI, and waist to height ratio of participants were significantly higher in the PreDM/HTN group but level of education was significantly lower. Furthermore, baseline characteristics of the participants for incident HTN and incident CKD are shown in Tables S1 and S2.

The calculated median follow-ups (interquartile range) were 11.7 (8.39–13.21) for incident T2DM, 10.1 (7.13–12.9) for incident HTN, and 11.0 (7.61–12.9) for incident CKD. Table 2 represents the event numbers and incidence rates per 1000 person-years of follow-up for each outcome according to glucose tolerance and blood pressure categories. Accordingly, the overall incidence rate for T2DM, HTN, and CKD was 12.2, 29.8, and 24.8 per 1000/person-years during follow-up. Of the total 2123 incident cases of HTN, 1519 (71.6%) were new cases, 504 (23.7%) had drug-treated and controlled HTN (ie, blood pressure <140/90), and 100 (4.7%) had drug-treated uncontrolled HTN. Results of age and sex adjusted models and multivariable Cox proportional hazard models for incident T2DM, HTN, and CKD are shown in Table 3. As shown in the multivariable adjusted model for incident T2DM, the HRs (HR [95% CI]) were ranging from 1.34 (1.06–1.69) of NGT/PreHTN to 7.22 (5.71–9.12) of PreDM/HTN. In the sensitivity analysis, when PreDM/NBP was considered as reference, the HR (95% CI) of PreDM/HTN was significantly higher while HRs of NGT/PreHTN and NGT/HTN were significantly lower.

For incident HTN, HRs (95% CI) were ranging from 1.25 (1.02–1.54) of PreDM/NBP to 3.69 (3.08–4.41) of T2DM/PreHTN. Furthermore, applying NGT/PreHTN as the reference group, we did not find any significant advantage for other groups for prediction of incident HTN, while PreDM/NBP showed a significantly lower risk.

For incident CKD, significant risks were found for T2DM/PreHTN (HR [95% CI]: 1.37 [1.11–1.70]), T2DM/NBP (1.28 [1.09–1.51]), T2DM/HTN (1.52 [1.24–1.86]), and NGT/HTN (1.38 [1.03–1.86]). Furthermore, PreDM/HTN showed a marginally significant risk (1.19 [0.98–1.43], $P=0.06$). Schoenfeld's global test of residuals showed no significant interactions with time for study variables.

Table 1. Baseline Characteristics of the Study Participants for Incident Diabetes, Tehran Lipid and Glucose Study, 1999–2015

Variables	NGT/NBP	PreDM/NBP	NGT/PreHTN	PreDM/PreHTN	NGT/HTN	PreDM/HTN	*P*-Value	Total N=8231
Age, y	35.4 (10.9)	42.8 (11.7)	40.4 (13.2)	46.5 (12.6)	50.8 (13.5)	55.0 (11.3)	<0.001	40.9 (13.6)
Sex (female), %	59.7	55.6	51.8	52.2	53.9	58.6	<0.001	56.2
BMI	25.1 (4.24)	26.9 (4.08)	27.0 (4.24)	28.6 (4.49)	28.4 (4.55)	29.5 (4.68)	<0.001	26.6 (4.59)
WHtR	0.51 (0.07)	0.55 (0.07)	0.54 (0.07)	0.57 (0.07)	0.57 (0.07)	0.6 (0.07)	<0.001	0.54 (0.07)
TG/HDL-C ratio	1.54 (1.25)	2.28 (2.65)	1.98 (1.60)	2.55 (2.57)	2.15 (1.50)	2.52 (2.15)	<0.001	1.91 (1.72)
TC, mmol/L	4.92 (1.08)	5.40 (1.11)	5.29 (1.09)	5.67 (1.13)	6.01 (1.17)	5.62 (1.18)	<0.001	5.25 (1.16)
LDL-C, mmol/L	3.10 (0.89)	3.46 (0.89)	3.38 (0.88)	3.61 (0.94)	3.87 (0.94)	3.62 (0.94)	<0.001	3.34 (0.93)
FH-CVD, %	24.4	35.2	24.9	31.6	21.9	28.8	<0.001	25.6
Education, %	—	—	—	—	—	—	<0.001	
0 to 5 years	17.6	31.4	28.3	42.7	49.9	62.5	—	29.7
6 to 12 years	64.7	55.6	56	44.8	40	30.7	—	55.5
>12 years	17.6	13	15.6	12.3	10	6.7	—	14.7
Smoking status	—	—	—	—	—	—	<0.001	
Current smokers, %	15.6	17	12.4	12.8	4.6	8.6	—	13.1
Past smokers, %	6.7	8.6	9.6	8.9	13.7	12.1	—	8.8
Nonsmokers, %	77.8	74.4	78	78.3	81.8	79.4	—	78.1
Physically active, %	28.4	26.8	27.8	26.1	25.7	30.1	<0.001	28

Physically active was defined as participating in a vigorous physical activity at least 3 days per week or achieving a minimum of at least 600 MET (metabolic equivalent task)-minutes per week. Data are mean (SD) or frequency. *P*-values were calculated by ANOVA or Mann–Whitney tests as appropriate. BMI indicates body mass index; FH-CVD, family history of type 2 diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; TG/HDL-C, triglycerides/high density lipoprotein cholesterol ratio; NBP, normal blood pressure; NGT, normal glucose tolerance; PreDM, prediabetes; PreHTN, prehypertension; TC, total cholesterol; WHtR, waist/height ratio.

Results of the sensitivity analysis with multiple imputed baseline missing data and inverse probability weighting in the Cox regression analysis are presented in Table 4. As shown, the median number of included participants in each analysis was higher and while the selection bias for lost to follow-up cases has been taken into account, the pattern of HRs and their 95% CIs approximately remained the same as those in Table 3.

Discussion

During our long-term study, we examined the impact of different combinations of glucose tolerance and blood pressure status on incident T2DM, HTN, and CKD. Regarding incident T2DM, we showed that different combinations had significant risks up to 7-fold for PreDM/HTN compared to

Table 2. Incidence Rates of T2DM, HTN, and CKD, Per 1000 Person-Years in Categories of Glucose Tolerance and Blood Pressure

	Incident T2DM		Incident HTN		Incident CKD	
Categories	Events/Total	Incidence/1000 Person-Years	Events/Total	Incidence/1000 Person-Years	Events/Total	Incidence/1000 Person-Years
NGT/NBP	162/3611	4.06	462/3629	11.9	547/3459	15.0
PreDM/NBP	150/523	30.3	127/530	23.7	112/473	23.5
NGT/PreHTN	155/2012	6.97	895/2027	50.0	393/1821	20.7
PreDM/PreHTN	245/640	42.5	351/650	67.3	171/546	31.4
PreDM/HTN	252/592	52.5	—	—	186/399	55.2
T2DM/PreHTN	—		213/343	94.4	128/274	55.4
NGT/HTN	97/853	10.84	—	—	254/642	43.6
T2DM/NBP	—	—	75/190	48.1	56/154	42.6
T2DM/HTN	—	—	—	—	154/291	69.4
Total	1061/8231	12.2	2123/7369	29.8	2001/8059	24.8

Tehran Lipid and Glucose Study, 1999–2015. CKD indicates chronic kidney disease; HTN, hypertension; NBP, normal blood pressure; NGT, normal glucose tolerance; PreDM, prediabetes; PreHTN, prehypertension; T2DM, type 2 diabetes.

Table 3. Age- and Sex-Adjusted Plus Multivariable Adjusted Hazard Ratios (95% CI) of the Categories of Glucose Tolerance and Blood Pressure in Relation to Incident T2DM, HTN, and CKD

Categories	Models	Incident T2DM N=8231	Incident HTN N=7369	Incident CKD N=8059
NGT/NBP		Reference	Reference	Reference
PreDM/NBP	Age/sex-adjusted	7.13 (5.69–8.92)	1.51 (1.24–1.84)	1.03 (0.84–1.27)
	Multivariable	5.58 (4.41–7.05)	1.25 (1.02–1.54)*	1.04 (0.84–1.28)
NGT/PreHTN	Age/sex-adjusted	1.63 (1.31–2.04)	3.73 (3.33–4.18)	1.00 (0.88–1.15)
	Multivariable	1.34 (1.06–1.69)†	3.28 (2.91–3.69)	1.01 (0.88–1.16)
PreDM/PreHTN	Age/sex-adjusted	9.67 (7.87–11.87)	4.08 (3.54–4.71)	1.09 (0.91–1.30)
	Multivariable	6.44 (5.17–8.01)	3.24 (2.78–3.76)	1.07 (0.89–1.29)
PreDM/HTN	Age/sex-adjusted	11.03 (8.85–13.7)	—	1.16 (0.97–1.39)
	Multivariable	7.22 (5.71–9.12)†	—	1.19 (0.98–1.43)‡
T2DM/PreHTN	Age/sex-adjusted	—	4.73 (3.99–5.61)	1.39 (1.14–1.69)
	Multivariable	—	3.69 (3.08–4.41)	1.37 (1.11–1.70)
NGT/HTN	Age/sex-adjusted	2.30 (1.77–3.00)	—	1.28 (1.10–1.50)
	Multivariable	1.65 (1.26–2.17)†	—	1.38 (1.03–1.86)
T2DM/NBP	Age/sex-adjusted	—	2.56 (2.01–3.28)	1.32 (1.00–1.75)
	Multivariable	—	1.92 (1.47–2.51)*	1.28 (1.09–1.51)
T2DM/HTN	Age/sex-adjusted	—	—	1.45 (1.20–1.75)
	Multivariable	—	—	1.52 (1.24–1.86)

Tehran Lipid and Glucose Study, 1999–2015. Cox proportional hazard models were used to calculate hazard ratios and 95% CI. The multivariable model is adjusted with age, sex, body mass index, waist/height ratio, triglycerides/high-density lipoprotein cholesterol ratio, education level, smoking status, and physical activity status. Moreover, the family history of diabetes entered the model for incident diabetes and family history of premature coronary artery disease for incident hypertension. CKD, chronic kidney disease; HTN indicates hypertension; NBP, normal blood pressure; NGT, normal glucose tolerance; PreDM, prediabetes; PreHTN, prehypertension; T2DM, type 2 diabetes.

*P-value to compare the hazard ratios of the multivariable models for incident HTN using NGT/Pre-HTN as reference was <0.001.

†P-value to compare the hazard ratios of the multivariable models for incident T2DM using Pre-DM/NBP as reference was <0.05.

‡P=0.06.

NGT/NBP. Furthermore, PreDM/HTN was significantly associated with increased risk of T2DM compared with PreDM/NBP. It should be highlighted that NGT/PreHTN was also significantly related to incident T2DM. As for incident HTN, all groups had significant risk while PreDM/NBP showed a marginally significant risk; however, adding PreDM or T2DM to PreHTN did not yield any higher risks. Generally, for incident CKD, presence of HTN or T2DM in any category, with or without PreDM or PreHTN, appeared as a significant predictor.

Very few studies have investigated the combined effects of blood glucose and blood pressure on incident T2DM, HTN, or CKD. It is well known that PreDM and HTN are risk factors for incident T2DM.[31] However, there are different findings among populations regarding the impact of PreHTN on developing T2DM. In our study, PreHTN and HTN alone were related to increased risk of T2DM about 34% and 65%. From the total of 1061 new cases of incident T2DM, only 180 individuals (17%) had a history of β-blocker and/or diuretic consumption before the occurrence of T2DM. From these individuals, 15 (8.3%), 38 (21.1%), and 127 (70.6%) were normotensive, prehypertensive, and hypertensive at baseline, respectively. Hence, considering the low rate of introduction of β-receptor blockers or diuretics for prehypertensive individuals (as important diabetogenic drugs[32]), it is very unlikely that these medications contribute significantly to incident T2DM. Researchers of The Framingham Offspring Study demonstrated that blood pressures ≥130/85 mm Hg (which includes those with PreHTN) or receiving treatment for HTN in a complex clinical model had 58% risk for incident T2DM with a score of 2 in the prediction model.[33] Among the adult population of Tehran, neither SBP nor DBP were risk factors for incident T2DM[16]; similar results were observed for incidence of PreDM and its different phenotypes.[13] In addition, in a study by Mullican et al in the San Antonio Heart Study, the relation of PreHTN with incident T2DM was no longer significant after adjusting with markers of insulin resistance and obesity.[10] Nonetheless, in a study by Kramer et al during 8 years of follow-up on an elderly population, PreHTN and HTN were associated with incident T2DM independent of BMI or insulin resistance.[34] In a study by Qiu et al, HTN alone did not have a significant risk for T2DM while

Table 4. Hazard Ratios (95% CI) of the Cox Regression Analyses With Inverse Probability Weighting With Multiple Imputed Baseline Missing Data for Categories of Glucose Tolerance and Blood Pressure in Relation to Incident T2DM, HTN, and CKD

Categories	Models	Incident T2DM N=9107*	Incident HTN N=8174*	Incident CKD N=8958*
NGT/NBP		Reference	Reference	Reference
PreDM/NBP	Age/sex-adjusted	6.36 (5.22–7.74)	1.5 (1.26–1.79)	1.05 (0.87–1.26)
	Multivariable	4.98 (4.08–6.07)	1.32 (1.11–1.58)	1.03 (0.86–1.24)
NGT/PreHTN	Age/sex-adjusted	1.56 (1.29–1.89)	3.61 (3.27–3.99)	1.04 (0.92–1.17)
	Multivariable	1.29 (1.06–1.56)	3.27 (2.96–3.62)	1.03 (0.92–1.16)
PreDM/PreHTN	Age/sex-adjusted	8.93 (7.47–10.6)	4.03 (3.56–4.57)	1.09 (0.93–1.28)
	Multivariable	5.96 (4.95–7.16)	3.31 (2.91–3.76)	1.08 (0.92–1.27)
PreDM/HTN	Age/sex-adjusted	9.81 (8.1–11.8)	—	1.2 (1.02–1.4)
	Multivariable	6.33 (5.2–7.7)	—	1.19 (1.01–1.39)
T2DM/PreHTN	Age/sex-adjusted	—	4.66 (4.01–5.41)	1.41 (1.19–1.69)
	Multivariable	—	3.66 (3.14–4.26)	1.41 (1.17–1.68)
NGT/HTN	Age/sex-adjusted	2.24 (1.79–2.8)	—	1.33 (1.16–1.52)
	Multivariable	1.6 (1.28–2.01)	—	1.31 (1.13–1.5)
T2DM/NBP	Age/sex-adjusted	—	2.52 (2.03–3.13)	1.36 (1.06–1.73)
	Multivariable	—	2.04 (1.64–2.55)	1.36 (1.06–1.75)
T2DM/HTN	Age/sex-adjusted	—	—	1.45 (1.23–1.71)
	Multivariable	—	—	1.45 (1.22–1.73)

Tehran Lipid and Glucose Study, 1999–2015. Cox proportional hazard models with Inverse Probability Weighting were used to calculate hazard ratios and 95% CI. The multivariable model is adjusted with age, sex, body mass index, waist/height ratio, triglycerides/high-density lipoprotein cholesterol ratio, education level, smoking status, and physical activity status. Moreover, the family history of diabetes entered the model for incident diabetes and family history of premature coronary artery disease for incident hypertension. CKD, chronic kidney disease; HTN, hypertension; NBP, normal blood pressure; NGT, normal glucose tolerance; PreDM, prediabetes; PreHTN, prehypertension; T2DM, type 2 diabetes.
*Median number of cases between 20 imputed data sets.

PreDM plus HTN resulted in a higher risk for incident T2DM.[7] Several studies in small selected populations have shown that T2DM and HTN can share certain types of gene polymorphism[35–38]; however, a recent study on the data of the genome-wide association studies has found an overlap between SBP and type 1 diabetes, but not T2DM.[39] Considering the mentioned studies, our results showed that although PreDM alone is a strong risk factor for developing T2DM, when combined with HTN, they have a significantly stronger impact on incident T2DM; however, presence of PreHTN besides PreDM was not associated with an increased risk.

Concerning incident HTN, insulin resistance has been shown to be related to the development of HTN in the adult population of Tehran.[40] In the current study, the presence of PreDM or T2DM alongside PreHTN was not related to an increased risk of developing HTN. The risk observed for incident HTN in the PreDM/NBP and T2DM/NBP groups might be attributable to the relationship between insulin resistance and HTN.[41] In a cohort of Chinese population, during a median follow-up of 6.15 years, a FPG ≥111 mg/dL and SBP ≥120 mm Hg had scores of 1 and >11 for incident HTN, respectively.[42] In accordance with other studies,[43,44] we highlighted that PreHTN is a strong risk factor leading to incident HTN and its relation is not affected by adding the data of glucose tolerance status. In a meta-analysis of the relation between hyperinsulinemia and incident HTN, comparison of the highest with the lowest quantile of fasting insulin concentrations showed a pooled relative risk of 63% for HTN when adjusting for FPG levels.[45] We extended the results of previous studies by showing that while PreDM as a surrogate of insulin resistance had a 32% risk for incident HTN, it did not increase the predictive power of PreHTN.

To the best of our knowledge, this is the first study investigating the combined effects of different combinations of glucose tolerance and blood pressure status on the development of CKD. In our study, generally, presence of HTN and/or T2DM, with/without the presence of PreDM or PreHTN, had independent compelling influence on the risk of future CKD. However, PreDM and/or PreHTN, separately or combined, did not have any significant effects in prediction of CKD. In a meta-analysis of cohort studies, both HTN and PreHTN were independent predictors of decreased GFR.[19] Furthermore, in another meta-analysis, PreHTN was

associated with incident end-stage renal disease and the increased risk was largely driven by high-range PreHTN.[46] We have previously shown that known T2DM and HTN were significant risk factors of incident CKD, while the presence of PreDM and PreHTN was related to about 20% increased risk, which did not reach a significant level.[17] On the other hand, in a study of the Framingham Offspring population, HTN did not increase the risk of developing CKD over 18.5 years.[47] Several cohort studies with 4 to 10 years of follow-up indicated that PreDM was not associated with incident CKD or reduced GFR when adjusted for cardiometabolic factors.[17,18] However, in a prospective study by Melsom et al, PreDM independently predicted the development of glomerular hyperfiltration and albuminuria.[48] Additionally, in another study dysglycemia (impaired fasting glucose and T2DM) was the most significant predictor of prevalent CKD.[49]

Our study has some limitations. First, we measured the baseline characteristics of the participants only once; hence, misclassification of potential risk factors such as blood pressure categories might attenuate our estimates while use of more precise methods such as 24-hour ambulatory blood pressure measurement can result in more accurate calculations of risk. In addition, we based our diagnosis of CKD on a single estimate of eGFR, which we acknowledge tends to overestimate the incidence of kidney disease. Estimated GFR measurements show a high degree of intraindividual variability and preferably require second measurements to correctly characterize kidney function. The use of successive eGFR measures, had they been obtainable, would likely have reduced the incidence of CKD, but would have not attenuated the association of the different groups of glucose tolerance and blood pressure with the outcome. Furthermore, most studies of CKD, epidemiologic and interventional, use single serum creatinine measurements. Moreover, albuminuria was not assessed and measured in TLGS, which could be used to define CKD. Second, we did not validate the CKD-EPI equation in a local population, and this could also lead to an overestimation in the incidence of CKD. Third, we did not have enough statistical power to stratify our analysis according to sex. Fourth, this study has been conducted on a sample of Iranian population and further studies should be conducted to determine whether our findings can be applicable to other populations. Finally, as the nature of observational studies dictates, no causality can be determined between a risk factor and an outcome.

On the other hand, a strength of this study is that, to the best of our knowledge, this is the first study to investigate the impact of different combinations of glycemic levels and blood pressure status with incident T2DM, HTN, and CKD in a long-term population-based cohort. Also, the reasonable size of population, length of follow-up, and use of actual measurements of variables rather than self-reported data are other strengths of this study. In addition, we used both FPG and 2 h-PCPG to categorize our participants into PreDM or NGT groups.

In conclusion, considering incident T2DM, prediabetic individuals with HTN are at a higher risk compared to the individuals with PreDM alone, while the presence of PreHTN was not associated with increased risk of developing T2DM. These results indicate that more attention should be paid to the presence of HTN in prediabetic individuals. Regarding incident HTN, in individuals with PreHTN, adding the data of glucose tolerance does not affect the progression risk. Finally, both HTN and T2DM were predictors of CKD while their preceding states (PreHTN and PreDM), alone or in combination, are not related to incident CKD. Last but not least, during more than a decade of follow-up, despite a large incidence of PreDM and PreHTN,[13,14] we did not confirm that combination of these predisease states leads to the higher risk of T2DM, HTN, and CKD.

While it is certainly useful to prevent important risk factors such as T2DM, HTN, and CKD, preventing clinically significant cardiovascular events is of greater priority. Hence, other prospective studies are needed to examine the impact of different combinations of glucose tolerance and blood pressure status on cardiovascular and mortality events.

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Disclosures

None.

References

1. Wang W, Lee ET, Fabsitz RR, Devereux R, Best L, Welty TK, Howard BV. A longitudinal study of hypertension risk factors and their relation to cardiovascular disease: the Strong Heart Study. *Hypertension*. 2006;47:403–409.
2. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang Y-H, Stevens GA. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet*. 2011;378:31–40.
3. Stahl CH, Novak M, Lappas G, Wilhelmsen L, Björck L, Hansson P-O, Rosengren A. High-normal blood pressure and long-term risk of type 2 diabetes: 35-year prospective population based cohort study of men. *BMC Cardiovasc Disord*. 2012;12:89.
4. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. *Lancet*. 2012;380:601–610.
5. Group TS. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care*. 2013;36:1735–1741.
6. Gupta A, Greenway F, Cornelissen G, Pan W, Halberg F. Prediabetes is associated with abnormal circadian blood pressure variability. *J Hum Hypertens*. 2008;22:627–633.
7. Qiu M, Shen W, Song X, Ju L, Tong W, Wang H, Zheng S, Jin Y, Wu Y, Wang W. Effects of prediabetes mellitus alone or plus hypertension on subsequent occurrence of cardiovascular disease and diabetes mellitus longitudinal study. *Hypertension*. 2015;65:525–530.
8. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. *Lancet*. 2012;379:2279–2290.

9. Stokes A, Mehta NK. Mortality and excess risk in US adults with pre-diabetes and diabetes: a comparison of two nationally representative cohorts, 1988–2006. *Popul Health Metr*. 2013;11:3.
10. Mullican DR, Lorenzo C, Haffner SM. Is prehypertension a risk factor for the development of type 2 diabetes? *Diabetes Care*. 2009;32:1870–1872.
11. Zhang Y, Lee ET, Devereux RB, Yeh J, Best LG, Fabsitz RR, Howard BV. Prehypertension, diabetes, and cardiovascular disease risk in a population-based sample: the Strong Heart Study. *Hypertension*. 2006;47:410–414.
12. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42:1206–1252.
13. Hadaegh F, Derakhshan A, Zafari N, Khalili D, Mirbolouk M, Saadat N, Azizi F. Pre-diabetes tsunami: incidence rates and risk factors of pre-diabetes and its different phenotypes over 9 years of follow-up. *Diabet Med*. 2015. doi: 10.1111/dme.13034. Available at: http://onlinelibrary.wiley.com/wol1/doi/10.1111/dme.13034/abstract. Accessed August 16, 2016.
14. Hadaegh F, Hasheminia M, Abdi H, Khalili D, Bozorgmanesh M, Arshi B, Azizi F. Prehypertension tsunami: a decade follow-up of an Iranian adult population. *PLoS One*. 2015;10:e0139412.
15. Bozorgmanesh M, Hadaegh F, Mehrabi Y, Azizi F. A point-score system superior to blood pressure measures alone for predicting incident hypertension: Tehran Lipid and Glucose Study. *J Hypertens*. 2011;29:1486–1493.
16. Derakhshan A, Sardarinia M, Khalili D, Momenan AA, Azizi F, Hadaegh F. Sex specific incidence rates of type 2 diabetes and its risk factors over 9 years of follow-up: Tehran Lipid and Glucose Study. *PLoS One*. 2014;9:e102563.
17. Tohidi M, Hasheminia M, Mohebi R, Khalili D, Hosseinpanah F, Yazdani B, Nasiri AA, Azizi F, Hadaegh F. Incidence of chronic kidney disease and its risk factors, results of over 10 year follow up in an Iranian cohort. *PLoS One*. 2012;7:e45304.
18. Fox CS, Larson MG, Leip EP, Meigs JB, Wilson PW, Levy D. Glycemic status and development of kidney disease: the Framingham Heart Study. *Diabetes Care*. 2005;28:2436–2440.
19. Garofalo C, Borrelli S, Pacilio M, Minutolo R, Chiodini P, De Nicola L, Conte G. Hypertension and prehypertension and prediction of development of decreased estimated GFR in the general population: a meta-analysis of cohort studies. *Am J Kidney Dis*. 2016;67:89–97.
20. Azizi F, Ghanbarian A, Momenan AA, Hadaegh F, Mirmiran P, Hedayati M, Mehrabi Y, Zahedi-Asl S. Prevention of non-communicable disease in a population in nutrition transition: Tehran Lipid and Glucose Study phase II. *Trials*. 2009;10:5.
21. Association AD. Standards of medical care in diabetes—2013. *Diabetes Care*. 2013;36:S11.
22. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137–147.
23. Matsushita K, Selvin E, Bash LD, Astor BC, Coresh J. Risk implications of the new CKD epidemiology collaboration (CKD-EPI) equation compared with the MDRD study equation for estimated GFR: the atherosclerosis risk in communities (ARIC) study. *Am J Kidney Dis*. 2010;55:648–659.
24. Little RJ. A test of missing completely at random for multivariate data with missing values. *J Am Stat Assoc*. 1988;83:1198–1202.
25. Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2011. Available at: https://www.jstatsoft.org/article/view/v045i03. Accessed August 16, 2016.
26. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377–399.
27. Bodner TE. What improves with increased missing data imputations? *Struct Equ Modeling*. 2008;15:651–675.
28. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res*. 2013;22:278–295.
29. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Hoboken, NJ: John Wiley & Sons; 2004.
30. Little RJ, Rubin DB. *Statistical Analysis With Missing Data*. Hoboken, NJ: John Wiley & Sons; 2014.
31. Association AD. Standards of medical care in diabetes mellitus. 2016. *Diabetes Care*. 2015;39:S13–S22.
32. Cooper-DeHoff RM, Bird ST, Nichols GA, Delaney JA, Winterstein AG. Antihypertensive drug class interactions and risk for incident diabetes: a nested case–control study. *J Am Heart Assoc*. 2013;2:e000125 doi: 10.1161/JAHA.113.000125.
33. Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. *Arch Intern Med*. 2007;167:1068–1074.
34. Kramer CK, von Mühlen D, Barrett-Connor E. Mid-life blood pressure levels and the 8-year incidence of type 2 diabetes mellitus: the Rancho Bernardo Study. *J Hum Hypertens*. 2010;24:519–524.
35. Zhuang L, Zhao Y, Zhao W, Li M, Yu M, Lu M, Zhang R, Ge X, Zheng T, Li C, Yin J, Yin J, Bao Y, Liu L, Jia W, Liu Y. The E23K and A190A variations of the KCNJ11 gene are associated with early-onset type 2 diabetes and blood pressure in the Chinese population. *Mol Cell Biochem*. 2015;404:133–141.
36. Koo BK, Cho YM, Park BL, Cheong HS, Shin HD, Jang HC, Kim SY, Lee HK, Park KS. Polymorphisms of KCNJ11 (Kir6.2 gene) are associated with type 2 diabetes and hypertension in the Korean population. *Diabet Med*. 2007;24:178–186.
37. Munoz-Barrios S, Guzman-Guzman IP, Munoz-Valle JF, Salgado-Bernabe AB, Salgado-Goytia L, Parra-Rojas I. Association of the HindIII and S447X polymorphisms in LPL gene with hypertension and type 2 diabetes in Mexican families. *Dis Markers*. 2012;33:313–320.
38. Ramachandran V, Ismail P, Stanslas J, Shamsudin N, Moin S, Mohd Jas R. Association of insertion/deletion polymorphism of angiotensin-converting enzyme gene with essential hypertension and type 2 diabetes mellitus in Malaysian subjects. *J Renin Angiotensin Aldosterone Syst*. 2008;9:208–214.
39. Andreassen OA, McEvoy LK, Thompson WK, Wang Y, Reppe S, Schork AJ, Zuber V, Barrett-Connor E, Gautvik K, Aukrust P. Identifying common genetic variants in blood pressure due to polygenic pleiotropy with associated phenotypes. *Hypertension*. 2014;63:819–826.
40. Arshi B, Tohidi M, Derakhshan A, Asgari S, Azizi F, Hadaegh F. Sex-specific relations between fasting insulin, insulin resistance and incident hypertension: 8.9 years follow-up in a Middle-Eastern population. *J Hum Hypertens*. 2015;29:260–267.
41. DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;14:173–194.
42. Chien KL, Hsu HC, Su TC, Chang WT, Sung FC, Chen MF, Lee YT. Prediction models for the risk of new-onset hypertension in ethnic Chinese in Taiwan. *J Hum Hypertens*. 2011;25:294–303.
43. Gupta AK, McGlone M, Greenway FL, Johnson WD. Prehypertension in disease-free adults: a marker for an adverse cardiometabolic risk profile. *Hypertens Res*. 2010;33:905–910.
44. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *JAMA*. 2002;287:1003–1010.
45. Xun P, Wu Y, He Q, He K. Fasting insulin concentrations and incidence of hypertension, stroke, and coronary heart disease: a meta-analysis of prospective cohort studies. *Am J Clin Nutr*. 2013;98:1543–1554.
46. Huang Y, Cai X, Zhang J, Mai W, Wang S, Hu Y, Ren H, Xu D. Prehypertension and incidence of ESRD: a systematic review and meta-analysis. *Am J Kidney Dis*. 2014;63:76–83.
47. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. *JAMA*. 2004;291:844–850.
48. Melsom T, Schei J, Stefansson VTN, Solbu MD, Jenssen TG, Mathisen UD, Wilsgaard T, Eriksen BO. Prediabetes and risk of glomerular hyperfiltration and albuminuria in the general nondiabetic population: a prospective cohort study. *Am J Kidney Dis*. 2016;67:841–850.
49. Whaley-Connell A, Pavey BS, McCullough PA, Saab G, Li S, McFarlane SI, Chen SC, Vassalotti JA, Collins AJ, Bakris G. Dysglycemia predicts cardiovascular and kidney disease in the kidney early evaluation program. *J Clin Hypertens*. 2010;12:51–58.

SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of the study participants for incident hypertension. Tehran Lipid and Glucose Study, 1999-2015.

Variables	NGT/NBP	PreDM/NBP	NGT/PreHTN	PreDM/PreHTN	T2DM/PreHTN	T2DM/NBP	P Value	Total N=7369
Age	35.4 (10.9)	42.9 (11.6)	40.4 (13.3)	46.5 (12.7)	52.3 (11.0)	49.8 (11.8)	<0.001	39.5 (12.8)
Sex (Female), %	59.6	55.8	51.8	52.3	57.7	51.1	<0.001	56.2
BMI	25.1 (4.24)	26.9 (4.06)	27.0 (4.26)	28.6 (4.50)	28.6 (4.23)	27.4 (4.36)	<0.001	26.3 (4.45)
WHtR	0.51 (0.07)	0.55 (0.07)	0.54 (0.72)	0.57 (0.07)	0.59 (0.06)	0.57 (0.07)	<0.001	0.53 (0.07)
TG/HDL-C ratio	1.54 (1.25)	2.28 (2.64)	1.98 (1.60)	2.54 (2.55)	2.91 (2.14)	3.29 (5.23)	<0.001	1.91 (1.91)
TC, mmol/L	4.92 (1.08)	5.41 (1.11)	5.29 (1.09)	5.65 (1.13)	5.82 (1.16)	5.76 (1.16)	<0.001	5.19 (1.14)
LDL-C, mmol/L	3.1 (0.89)	3.47 (0.89)	3.38 (0.88)	3.6 (0.94)	3.68 (0.93)	3.64 (0.90)	<0.001	3.28 (0.91)
FH-CVD, %	14.4	15.5	14.9	16	19.5	18.9	<0.001	15.1
Education, %	-	-	-	-	-	-	<0.001	-
0-5 years	17.6	31.7	28.6	42.6	53.9	51.6	-	26.4
6-12 years	64.8	55.5	55.8	44.8	39.4	41.1	-	58.1
>12 years	17.6	12.8	15.5	12.5	6.7	7.4	-	15.5
Smoking status	-	-	-	-	-	-	<0.001	-
Current smokers, %	15.5	17	12.3	12.6	10.8	20.5	-	14.4
Past smokers, %	6.7	8.7	9.7	9.1	11.7	8.9	-	8.2

Non-smokers, %	77.7	74.3	78	78.3	77.6	70.5	-	77.4
Physically active, %	28.5	26.4	27.8	26.3	27.4	27.9	<0.001	27.9

NGT, normal glucose tolerance; NBP, normal blood pressure; PreDM, prediabetes; PreHTN, prehypertension; T2DM, type 2 diabetes mellitus. BMI, body mass index; WHtR, waist/height ratio; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; FH-CVD, family history of premature cardiovascular disease. Physically active was defined as participating in a vigorous physical activity at least three days per week or achieving a minimum of at least 600 MET (metabolic equivalent task)-minutes per week. P values were calculated by ANOVA or Mann-Whitney tests as appropriate.

Table S2. Baseline characteristics of the study participants for incident chronic kidney disease. Tehran Lipid and Glucose Study, 1999-2015.

Variables	NGT/NBP	PreDM/NBP	NGT/PreHTN	PreDM/PreHTN	T2DM/PreHTN	PreDM/HTN	NGT/HTN	T2DM/NBP	T2DM/HTN	P Value	Total N=8059
Age	34.5 (10.1)	41.3 (10.8)	38.5 (12.0)	44.0 (11.5)	51.4 (11.0)	50.2 (10.2)	47.4 (11.2)	46.9 (12.7)	53.6 (9.57)	<0.001	39.9 (12.9)
Sex (Female), %	58.4	52.0	48.7	50.2	51.0	53.2	43.9	49.0	55.4	<0.001	53.6
BMI	24.9 (4.22)	26.9 (4.09)	26.8 (4.22)	28.7 (4.59)	29.4 (4.64)	28.6 (4.44)	27.1 (4.22)	28.3 (4.70)	30.2 (4.88)	<0.001	26.6 (4.64)
WHtR	0.50 (0.06)	0.54 (0.07)	0.54 (0.07)	0.57 (0.07)	0.60 (0.07)	0.59 (0.07)	0.56 (0.06)	0.57 (0.07)	0.62 (0.07)	<0.001	0.53 (0.07)
TG/HDL-C ratio	1.52 (1.23)	2.35 (2.79)	1.98 (1.64)	2.55 (2.68)	2.69 (2.49)	3.09 (2.27)	3.36 (5.78)	2.08 (1.45)	2.89 (2.43)	<0.001	1.98 (1.98)
TC, mmol/L	4.88 (1.05)	5.34 (1.08)	5.23 (1.07)	5.6 (1.11)	5.87 (1.17)	5.74 (1.17)	5.66 (1.27)	5.48 (1.12)	6.01 (1.28)	<0.001	5.21 (1.14)
LDL-C, mmol/L	3.06 (0.87)	3.42 (0.86)	3.32 (0.85)	3.55 (0.93)	3.74 (0.94)	3.61 (0.95)	3.58 (0.91)	3.51 (0.90)	3.82 (1.01)	<0.001	3.30 (0.91)
Education	-	-	-	-	-	-	-	-	-	<0.001	-
0-5 years	15.7	28.1	24.4	37.2	54.3	48.3	47.3	42.3	64.4	-	27.3
6-12 years	66.3	59.4	59.1	49.1	37.4	44.2	43.9	45.2	29.6	-	57.4
>12 years	18.0	12.5	16.5	13.7	8.3	7.5	8.8	12.5	6.0	-	15.2
Smoking status	-	-	-	-	-	-	-	-	-	<0.001	-
Current smokers, %	15.7	18.2	12.6	13	5.8	11.7	22.7	10	7.9	-	13.7
Past smokers, %	6.5	8.9	9.7	8.6	13.5	12	8.4	11.2	11.3	-	8.6

Non-smokers, %	77.8	72.9	77.8	78.4	80.7	76.3	68.8	78.8	80.8	-	77.6
Physically active, %	28.4	26.2	27.2	27.3	26.6	25.9	28.6	31.5	26.5	<0.001	28

NGT, normal glucose tolerance; NBP, normal blood pressure; PreDM, prediabetes; PreHTN, prehypertension; T2DM, type 2 diabetes mellitus; HTN, hypertension. BMI, body mass index; WHtR, waist/height ratio; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol. Physically active was defined as participating in a vigorous physical activity at least three days per week or achieving a minimum of at least 600 MET (metabolic equivalent task)-minutes per week. P values were calculated by ANOVA or Mann-Whitney tests as appropriate.