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
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. Also, both PreHTN and PreDM have been suggested as risk factors associated with decreased glomerular filtration rate (GFR). 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 3,427 second-phase recruits (2002–2005). A detailed description of the TLGS has been reported elsewhere. For the current study, after exclusion of 5,624 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 1,376 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 2,660 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 1,784 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 8,059 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. 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.

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. 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. 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 m² for >3 months. For this study, eGFR was estimated using the abbreviated prediction equation, provided by the CKD-EPI formula as follows:

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eGFR = 141 × min \((\text{serum creatinine}/\kappa, 1)^2\)
× max \((\text{serum creatinine}/\kappa, 1)^{-1.209}\)
× 0.993^{\text{age}} × 1.018 [if female]

In this equation, eGFR is expressed as mL/min per 1.73 m\(^2\), serum creatinine is expressed as mg/dL, \(\kappa\) is 0.7 for females and 0.9 for males, \(\alpha\) is \(-0.329\) for females and \(-0.411\) for males, min indicates the minimum of serum creatinine/\(\kappa\) or 1 and max indicates the maximum of serum creatinine/\(\kappa\) 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 \(\approx 17\%\) 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 \(\geq 20\) 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 inverted 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.
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 PreDM/NBP.
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. 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), 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. Among the adult population of Tehran, neither SBP nor DBP were risk factors for incident T2DM; similar results were observed for incidence of PreDM and its different phenotypes. 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. Nonetheless, in a study by Qi et al, HTN alone did not have a significant risk for T2DM while...
PreDM plus HTN resulted in a higher risk for incident T2DM. Several studies in small selected populations have shown that T2DM and HTN can share certain types of gene polymorphisms; 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. 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. 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. 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. In accordance with other studies, 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. We extended the results of previous studies by showing that while PreDM as a surrogate of insulin resistance had a 32% relative 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. Furthermore, in another meta-analysis, PreHTN was

### 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 | Incident HTN | Incident CKD |
|------------|--------------|---------------|---------------|---------------|
|            | Reference    | Reference     | Reference     | N=9107*       |
| 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.
associated with incident end-stage renal disease and the increased risk was largely driven by high-range PreHTN. 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. 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. 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. However, in a prospective study by Melsom et al, PreDM independently predicted the development of glomerular hyperfiltration and albuminuria. Additionally, in another study dysglycemia (impaired fasting glucose and T2DM) was the most significant predictor of prevalent CKD.

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 intrindividual variability and preferably require second measurements to correctly characterize kidney function. The use of successive eGFR measurements 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, 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.

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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.
| 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         |
|                      | 77.8 | 72.9 | 77.8 | 78.4 | 80.7 | 76.3 | 68.8 | 78.8 | 80.8 |   | 77.6 |
|----------------------|------|------|------|------|------|------|------|------|------|---|------|
| Non-smokers, %       |      |      |      |      |      |      |      |      |      |   |      |
| 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.