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ORIGINAL ARTICLE

Different combinations of glucose tolerance and blood pressure status and incident cardiovascular disease and all-cause mortality events

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The purpose of this study was to evaluate the effect of combinations of blood pressure and glucose tolerance status on cardiovascular and all-cause mortality. A total of 7619 participants aged ⩾30 years old were stratified to nine categories as follows: (1) normotension (NTN) and normal glucose tolerance (NGT) (reference group), (2) NTN and pre-diabetes mellitus (pre-DM), (3) NTN and DM, (4) pre-hypertension (pre-HTN) and NGT, (5) pre-HTN and pre-DM, (6) pre-HTN and DM, (7) HTN and NGT, (8) HTN and pre-DM and (9) HTN and DM. Cox proportional hazards were applied to calculate the multivariate hazard ratios (HRs) of different groups for outcomes. For all-cause mortality outcomes, prevalent cardiovascular disease (CVD) was also adjusted. In a median follow-up of 11.3 years, 696 CVD and 412 all-cause mortality events occurred. Among the population free from CVD at baseline ($n = 7249$), presence of HTN was associated with increased risk of CVD, regardless of glucose tolerance status with HRs of 1.97 (95% confidence interval (CI), 1.49–2.61), 2.25 (1.68–3.02) and 3.16 (2.28–4.37) for phenotypes of HTN and NGT, HTN and pre-DM and HTN and DM for CVD, respectively; corresponding HRs for all-cause mortality were 1.65 (95% CI, 1.15–2.37), 1.69 (1.15–2.49) and 2.73 (1.80–4.14), respectively. Phenotypes of NTN and pre-DM (1.48; 1.03–2.14) and NTN and DM (2.04; 1.06–3.92) were also associated with CVD and all-cause mortality, respectively. HTN was significantly associated with CVD/mortality events, regardless of glucose tolerance status. Blood pressure $<120/80$ mm Hg among pre-diabetic/diabetic population, not on antihypertensive medications, was generally associated with worse outcomes.

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INTRODUCTION

Hypertension (HTN) and diabetes mellitus (DM) are considered as main risk factors contributing for cardiovascular disease (CVD) and all-cause mortality.[1–3] Pre-hypertension (pre-HTN) and pre-diabetes (pre-DM) status are pre-disease states growing in the globe in the light of rapid growth of obesity and changing in nutritional status and physical activity.[4,5] Pre-HTN as originally defined by Joint National Committee 7[6] as 120 mm Hg ⩽ systolic blood pressure (SBP) <140 mm Hg or 80 mm Hg ⩽ diastolic blood pressure (DBP) <90 mm Hg is increasing worldwide reaching to incidence rate of 46% in some countries.[7] It is shown that pre-HTN status is associated with CVD[8] but not all-cause mortality.[9] Pre-DM as redefined by American Diabetes Association in 2003[10] as 5.55 mmol l^{-1} ⩽ fasting plasma glucose (FPG) <7 mmol l^{-1} or 7.77 mmol l^{-1} ⩽ 2 h post-challenge plasma glucose (2 h-PCPG) <11.1 mmol l^{-1} is also associated with increased risk of CVD and coronary heart disease (CHD) mortality in a recent meta-analysis.[11,12]

Furthermore, a recent study suggests that HTN and DM have distinct genomic profile and highlights that the genetic profile for several diseases combination might be markedly different from the isolated form of the disease,[13] showing the need for studies addressing the effect of pure and combined forms of the diseases. More importantly, studies show that presence of HTN is more frequent among diabetic individuals and vice versa, leading to high rate of macro and microvascular complications among these group of patients.[14,15] On the other hand, recently it was shown among untreated diabetic patients, the presence of blood pressure (BP) $<120/80$ mm Hg was associated with higher risk of all-cause mortality events compared with pre-hypertensive groups.[16]

To the best of our knowledge, there are few studies investigating the role of different combinations of glucose tolerance status (that is, normoglycemia, pre-DM and DM) and BP status (that is, normotension (NTN), pre-HTN and HTN) on CVD events,[17–19] and considering the lack of data in relation to all-cause mortality, this study was conducted in a large community-based cohort of the Tehran Lipid and Glucose Study to investigate the impact of different combinations of glucose and BP status on CVD and all-cause mortality events among Iranian adults, which could be used in designing appropriate health strategies.

PATIENTS AND METHODS

Study population

Tehran Lipid and Glucose Study is a community-based cohort study initiated between March 1999 and December 2001, and conducted on a representative sample of Tehranian population. Tehran Lipid and Glucose

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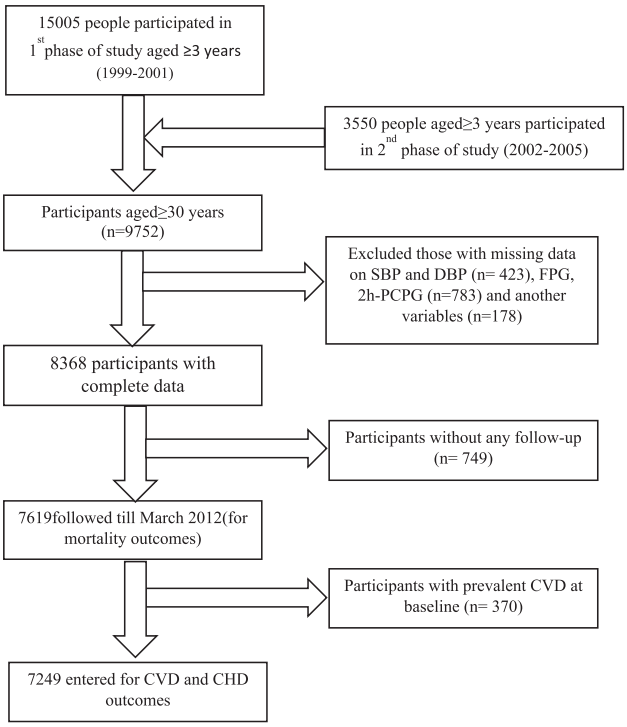

Figure 1. Selection of study participants, Tehran Lipid and Glucose Study (1999–2012).

Study carried out to determine the prevalence of various risk factors and their association with non-communicable diseases. Detailed descriptions of the study methods have been reported elsewhere;[20] to date, five phases of the study have been carried out (starting from 1999 to 2015 with 3-year intervals).

A total number of 15 005 of participants were entered during first phase (1999–2002) and 3550 during second phase of the study (2002–2005); among which 9752 participants aged $\geqslant 30$ years were considered in the current study. Exclusions included those with missing data on systolic or diastolic BP ($n=423$), FPG or 2 h-PCPG test ($n=783$), missing data on covariates ($n=178$) or without any follow-up data ($n=749$), leaving 7619 participants who were followed till March 2012, with a median of 11.3 years. Also, to investigate the impact of different combinations of glucose tolerance and BP status on incident CVD/CHD events, participants with prevalent CVD were excluded from the analysis, leaving 7249 participants (Figure 1).

The protocol of study was approved by ethics committee of the Shahid Beheshti University of Medical Sciences, and written informed consents were obtained from all participants.

Clinical and laboratory measurement

Participants were interviewed face-to-face by trained interviewer using a standard questionnaire; information documented included demographic data (sex, age and education status), smoking and family history of premature CVD plus history of medication use.

Details of anthropometric measures regarding height, weight, waist circumferences and hip circumference using standard protocols have been previously published elsewhere.[20] Body mass index (BMI) and waist-to-hip ratio were calculated by dividing weight (kg) to height (m^2) and waist circumference to hip, respectively.

A standardised mercury sphygmomanometer (calibrated by the Iranian Institute of Standards and Industrial Researches) was used to measure SBP and DBP on the right arm after a 15 min rest in the sitting position; for each participant, two measurements were performed and mean of two measurements was considered as the participant's BP.

After 12–14 h overnight fasting, a blood sample was taken from all participants and centrifuged within 30–45 min of collection. For the oral glucose tolerance test, 75 g glucose was administered orally to the subjects who did not use anti-diabetic medications, and plasma glucose was measured 2 h after. Details of laboratory assessments including FPG, 2 h-PCPG and total cholesterol have been reported elsewhere.[20]

Definition of terms

The participants were categorised according to their BP and diabetes status into nine categories as follows: (1) normal glucose tolerance (NGT) and NTN (reference group), (2) NTN and pre-DM, (3) NTN and DM, (4) pre-HTN and NGT (5) pre-HTN and pre-DM, (6) pre-HTN and DM, (7) HTN and NGT, (8) HTN and pre-DM and (9) HTN and DM. According to the Joint National Committee 7 definition,[6] HTN was defined as SBP $\geqslant 140$ mm Hg or DBP $\geqslant 90$ mm Hg or use of antihypertensive medication, and pre-HTN was defined as 120 mm Hg $\leqslant$ SBP < 140 mm Hg or 80 mm Hg $\leqslant$ DBP < 90 mm Hg. DM and pre-DM were defined according to American Diabetes Association criteria;[10] DM as FPG $\geqslant 7$ mmol l^{-1} or a 2 h-PCPG $\geqslant 11.1$ mmol l^{-1} or using anti-diabetic medication; pre-DM as 5.55 mmol l^{-1} $\leqslant$ FPG < 7 mmol l^{-1} or 7.77 mmol l^{-1} $\leqslant$ 2 h-PCPG < 11.1 mmol l^{-1}. Population with FPG < 5.55 mmol l^{-1} and 2 h-PCPG < 7.77 without using anti-diabetic medication was considered as NGT.

Hypercholesterolemia was defined as serum total cholesterol $\geqslant 6.21$ mmol l^{-1} or using lipid-lowering medication. We defined ever smoking as participants who had past or current usage of cigarettes or water pipe or pipe. Education was classified into three groups as follows: illiterate/primary school, under diploma and upper diploma.

Definition of outcomes

Details of cardiovascular data have been published elsewhere.[21] Briefly, participants were followed up by phone calls from a trained nurse every year regarding any medical event leading to their hospitalisation in the past year and then complimentary data were obtained by a trained physician during a home or hospital visit. Data then were evaluated by an outcome committee consisting of a principal investigator, an internist, an endocrinologist, an epidemiologist, a cardiologist, the physician who gathered data and other experts if needed. The committee then assigned a specific diagnosis for each event. Cases of CHD events included those with definite myocardial infarction (diagnostic electrocardiogram and biomarkers), probable myocardial infarction (positive electrocardiogram findings with cardiac symptoms or signs in the presence of negative or equivocal biomarker results), unstable angina pectoris (new cardiac symptoms or changing symptom patterns and positive electrocardiogram findings with normal biomarkers), and angiographically proven CHD or CHD death. CVD outcomes were considered as any CHD events, cerebrovascular accidents or CVD deaths.

Statistical analysis

Baseline characteristics of the participants were shown as mean (s.d.) and frequency (%) for continuous and categorical variables, respectively. Comparisons between different groups of glucose tolerance and blood pressure status regarding baseline characteristics were performed using one way analysis of variance or χ^2-tests, as appropriate.

Incidence rate of mortality with 95% confidence interval (CI) was calculated for each group by dividing the total number of incident mortality to the sum of person times of follow-up. Cox proportional hazards models were used to evaluate associations between each group with all-cause mortality. Survival time was calculated from the start of the follow-up period to the date of the first incident CVD/CHD or mortality event (failure). Censoring time was from the time of the individual's entrance to the study until loss to follow-up or end of the study, whichever happened first. We performed the analysis for CVD and CHD outcome in two models; model 1 was only adjusted for sex and age, while model 2 was further adjusted for other confounder variables including BMI, waist-to-hip ratio, smoking, hypercholesterolemia and education. Adjusted hazard ratios (HRs) were reported with 95% CI, considering NGT and NTN group as the reference. The assumption of Cox proportional hazard model was assessed graphically using Schoenfeld's residuals test.

We found no interaction between sex and different groups using likelihood ratio test (P-value = 0.214); hence the analyses were carried out in pooled sex samples to reach full statistical power. Furthermore, interactions of prevalent CVD and different groups were also examined in multivariate model for all-cause mortality and no interaction was found (P-value = 0.294); hence, the prevalent CVD was adjusted in multivariate analysis. All statistical analyses were performed using IBM SPSS (SPSS for Windows, Version 20.0.0, SPSS Inc., Chicago, IL, USA) and STATA version 12

Table 1. Baseline characteristics: Tehran Lipid and Glucose Study (1999–2012)

Variables	*NTN and NFG/ NGT*	*NTN and pre-DM*	*NTN and DM*	*Pre-HTN and NFG/ NGT*	*Pre-HTN and pre-DM*	*Pre-HTN and DM*	*HTN and NFG/ NGT*	*HTN and pre-DM*	*HTN and DM*	P-*value*
Number	2592	507	106	1675	649	203	922	650	315	
Number of available OGTT	2536	507	100	1648	649	201	900	650	307	
Age, years	40.96 (9.69)	45.20 (10.53)	50.71 (11.42)	45.39 (11.88)	48.63 (11.64)	51.13 (11.26)	53.78 (12.41)	55.80 (11.20)	58.16 (10.28)	< 0.0001
Sex, % (male)	1177 (45.41)	240 (47.34)	58 (54.72)	809 (48.30)	304 (46.84)	86 (42.36)	416 (45.12)	267 (41.08)	146 (46.35)	0.051
BMI (kg m^{-2})	25.78 (4.15)	27.05 (4.19)	28.04 (4.33)	27.49 (4.19)	28.79 (4.52)	29.11 (4.13)	28.52 (4.51)	29.60 (4.93)	29.79 (4.44)	< 0.0001
Waist to hip	0.85 (0.08)	0.89 (0.08)	0.93 (0.08)	0.88 (0.081)	0.91 (0.07)	0.93 (0.08)	0.91 (0.08)	0.92 (0.08)	0.95 (0.07)	< 0.0001
SBP (mm Hg)	105.36 (7.98)	107.51 (7.52)	109.16 (6.93)	121.38 (8.51)	123.43 (8.01)	125.56 (8.32)	142.04 (19.93)	144.67 (18.15)	149.36 (20.74)	< 0.0001
DBP (mm Hg)	69.73 (6.08)	70.76 (5.74)	70.68 (5.88)	80.71 (5.77)	80.49 (6.04)	80.37 (6.33)	90.27 (10.47)	89.90 (10.85)	88.64 (15.58)	< 0.0001
FPG (mmol l^{-1})	4.81 (0.38)	5.54 (0.51)	7.62 (2.63)	4.87 (0.38)	5.57 (0.53)	7.60 (2.44)	4.90 (0.36)	5.61 (0.57)	7.47 (2.54)	< 0.0001
2 h-PCPG (mmol l^{-1})	5.31 (1.15)	7.48 (1.73)	14.62 (5.20)	5.62 (1.15)	7.56 (1.80)	14.94 (4.61)	5.78 (1.14)	8.07 (1.57)	15.23 (4.85)	< 0.0001
TC (mmol l^{-1})	5.15 (1.07)	5.43 (1.10)	5.86 (1.16)	5.46 (1.09)	5.71 (1.13)	11.1 (2.90)	5.71 (1.18)	6.01 (1.16)	6.09 (1.44)	< 0.0001
Hypercholesterolemia (%)	419 (16.17)	117 (23.08)	40 (37.74)	400 (23.88)	200 (30.82)	69 (33.99)	306 (33.19)	291 (44.77)	151 (47.94)	< 0.0001
Ever smoking (%)	596 (22.99)	110 (21.70)	32 (30.19)	268 (16)	95 (14.64)	22 (10.84)	104 (11.28)	42 (6.64)	28 (8.89)	< 0.0001
Education status										
Above diploma	430 (16.59)	60 (11.83)	12 (11.32)	239 (14.27)	70 (10.79)	13 (6.40)	87 (9.44)	38 (5.85)	20 (6.35)	< 0.0001
Below diploma	1534 (59.18)	276 (54.44)	40 (37.74)	835 (49.85)	281 (43.30)	89 (43.84)	326 (35.36)	199 (30.62)	87 (27.62)	
Illiterate	628 (24.23)	171 (33.73)	54 (50.94)	601 (35.88)	298 (45.92)	101 (49.75)	509 (55.21)	413 (63.54)	208 (66.03)	

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; HTN, hypertension; OGTT, oral glucose tolerance test; Pre-DM, pre-diabetes; Pre-HTN, pre-hypertension; NFG, normal fasting glucose; NGT, normal glucose tolerance; NTN, normotension; SBP, systolic blood pressure; TC, total cholesterol; 2 h-PCPG, 2 h post-challenge plasma glucose. Hypercholesterolemia was defined as serum total cholesterol $\geqslant 6.21$ mmol l^{-1} or using lipid-lowering medication. Total number of participants with available 2 h-PCPG = 7518.

SE (StataCorp LP, College Station, TX, USA), and *P*-value < 0.05 was considered with statistical significance.

RESULTS

Baseline characteristics of participants according to their glucose tolerance and BP status have been presented in Table 1. Mean age of participants were 46.8 years and ~46% of them were males. There was significant differences in baseline characteristics, among groups including age, BMI, sex, waist-to-hip ratio, SBP, DBP, FPG, 2 h-PCPG, hypercholesterolemia, smoking and educational status. Baseline characteristics of participants with and without mortality events have been presented in Supplementary Table 1.

Over a median follow-up of 11.3 years, 696 CVD, 595 CHD and 412 all-cause mortality events occurred. As shown in Table 2, in multivariate-adjusted model, presence of HTN in any phenotype of glucose tolerance caused significant increase in CVD rates, with HRs of 1.97 (95% CI, 1.49–2.61), 2.25 (95% CI, 1.68–3.02) and 3.16 (95% CI, 2.28–4.37) in HTN and NGT, HTN and pre-DM and HTN and DM phenotypes, respectively; corresponding HRs of these groups for CHD were 1.87 (95% CI, 1.38–2.52), 2.04 (95% CI, 1.49–2.80) and 2.91 (95% CI, 2.05–4.13), respectively. Phenotypes of NTN and pre-DM and pre-HTN and DM showed significant risks in multivariate analysis (1.48 (95%CI, 1.03–2.14) and 1.71 (95% CI, 1.08–2.71)), for CVD events respectively; the latter group highlighted significant risk for CHD events (1.87 (95% CI, 1.16–2.99)).

As shown in Table 3 regarding mortality events as like as for CVD, in every glucose tolerance phenotypes, the presence of HTN increased the risk of mortality events with HRs of 1.65 (95% CI, 1.15–2.37), 1.69 (95% CI, 1.15–2.49) and 2.73 (95% CI, 1.80–4.14) for HTN and NGT, HTN and pre-DM, and HTN and DM, respectively, in multivariate-adjusted model. Furthermore, the NTN and DM groups had a 100% increased risk for mortality events (HR: 2.04 (1.06–3.92)). No other groups showed significant risk.

DISCUSSION

To the best of our knowledge, this is among the first studies to examine the impact of different combination of glucose tolerance and BP status with CVD and all-cause mortality during more than a decade follow-up. In comparison to the reference, the hypertensive groups in the presence of diabetes showed a significant risk of more than twofold for CVD/CHD and all-cause mortality events. Furthermore, the pre-HTN and DM group showed a significant risk of about 70% for CVD events. The NTN and DM group highlighted a 100% increased risk for mortality events. Finally, the NTN and pre-DM group showed about 50% increased risk in multivariate analysis for CVD/CHD events.

Although, DM and HTN are well-known risk factors for CVD and all-cause mortality events, population-based studies examining the impact of different combinations of glucose tolerance and BP status on these outcomes are scarce. Similar to our findings, a population-based study conducted in China showed significant risk for CVD events for HTN groups, whether *per se* alone or in the presence of glucose intolerance status.[18] In the current study, the presence of pre-HTN increased the risk of CVD by about 71% among the population with DM. The researchers of the Strong heart study showed HR > 2 for patients with DM in the presence of NTN or pre-HTN status only for CVD events.[17] Pre-HTN, as a pre-disease risk factor, was reported to be associated with CVD/CHD but not all-cause mortality events.[8] Among Iranian adults, we previously found that the risk of pre-HTN for CVD events was limited to middle aged population.[9] In another study conducted among Turkish population, it was also shown the independent risk of pre-HN for CHD as well as

Table 2. Incidence rate and hazard ratios for CVD and CHD events by blood pressure and glucose tolerance status: Tehran Lipid and Glucose Study (1999–2012)

	No of events	*Events/1000 person-years*	*95% CI*	*Sex- and age-adjusted model*			*Multivariate-adjusted model*		
				Hazard ratio	*95% CI*	P-*value*	*Hazard ratio*	*95% CI*	P-*value*
CVD event									
NTN and NFG/NGT	105	3.92	3.23–4.74	—	—	—	—	—	—
NTN and pre-DM	41	8.00	5.89–10.86	1.61	1.12–2.31	0.009	1.48	1.03–2.14	0.032
NTN and DM	13	13.16	7.64–19.67	1.92	1.07–3.43	0.027	1.59	0.89–2.85	0. 116
Pre-HTN and NFG/NGT	123	6.69	5.86–8.34	1.30	1.00–1.69	0.047	1.25	0.96–1.64	0.094
Pre-HTN and pre-DM	57	8.62	6.65–11.17	1.40	1.01–1.94	0.043	1.27	0.91–1.77	0.157
Pre-HTN and DM	24	12.45	8.34–18.57	1.90	1.21–2.98	0.005	1.71	1.08–2.71	0.021
HTN and NFG/NGT	131	15.95	13.44–18.93	2.11	1.61–2.77	0.000	1.97	1.49–2.61	< 0.0001
HTN and pre-DM	120	20.27	16.95–24.25	2.54	1.93–3.35	0.000	2.25	1.68–3.02	< 0.0001
HTN and DM	82	32.78	26.40–40.70	3.99	2.95–5.39	0.000	3.16	2.28–4.37	< 0.0001
Total	696	9.20	8.54–9.91	—	—	—	—	—	—
CHD event									
NTN and NFG/NGT	97	3.62	2.96–4.41	—	—	—	—	—	—
NTN and pre-DM	36	7.00	5.05–9.71	1.56	1.06–2.29	0.022	1.43	0.97–2.10	0.067
NTN and DM	11	11.11	6.15–2.00	1.86	0.99–3.48	0.052	1.51	0.81–2.85	0.192
Pre-HTN and NFG/NGT	107	6.07	5.02–7.33	1.27	0.96–1.68	0.086	1.21	0.91–1.61	0.171
Pre-HTN and pre-DM	50	7.53	5.711–9.94	1.38	0.98–1.96	0.062	1.24	0.87–1.77	0.224
Pre-HTN and DM	23	11.93	7.93–14.95	2.11	1.33–3.34	0.001	1.87	1.16–2.99	0.009
HTN and NFG/NGT	108	13.05	11.81–15.76	2.02	1.51–2.70	0.000	1.87	1.38–2.52	< 0.0001
HTN and pre-DM	96	16.01	13.11–19.56	2.34	1.74–3.16	0.000	2.04	1.49–2.80	< 0.0001
HTN and DM	67	26.53	20.88–33.70	3.77	2.72–5.23	0.000	2.91	2.05–4.13	< 0.0001
Total	595	7.84	7.23–8.49	—	—	—	—	—	—

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; NFG, normal fasting glucose; NGT, normal glucose tolerance; NTN, normotension; Pre-DM, pre-diabetes; Pre-HTN, pre-hypertension. Multivariate-adjusted model was adjusted for age, gender, body mass index, waist to hip, smoking, hypercholesterolemia and education.

Table 3. Incidence rate and hazard ratio for all-cause mortality by blood pressure and glucose tolerance status: Tehran Lipid and Glucose Study (1999–2012)

	No of events	*Events/1000 person-years*	*95% CI*	*Sex- and age-adjusted model*			*Multivariate-adjusted model*		
				Hazard ratio	*95% CI*	P-*value*	*Hazard ratio*	*95% CI*	P-*value*
NTN and NFG/NGT	56	2.02	1.55–2.63	—	—	—	—	—	—
NTN and pre-DM	19	3.45	2.20–5.41	1.17	0.69–1.97	0.554	1.23	0.73–2.09	0.421
NTN and DM	11	9.94	5.50–17.96	1.97	1.02–3.77	0.041	2.04	1.06–3.92	0.032
Pre-HTN and NFG/NGT	57	3.09	2.38–4.01	0.87	0.60–1.26	0.471	0.96	0.66–1.41	0.871
Pre-HTN and pre-DM	30	4.25	2.97–6.08	0.99	0.63–1.55	0.985	1.13	0.72–1.79	0.580
Pre-HTN and DM	13	6.09	3.54–10.50	1.19	0.65–2.19	0.567	1.35	0.72–2.52	0.339
HTN and NFG/NGT	96	9.74	7.98–11.90	1.50	1.06–2.12	0.020	1.65	1.15–2.37	0.006
HTN and pre-DM	71	10.06	7.97–12.70	1.45	1.01–2.09	0.044	1.69	1.15–2.49	0.007
HTN and DM	59	18.35	14.21–23.68	2.41	1.64–3.53	0.000	2.73	1.80–4.14	< 0.000
Total	412	5.02	4.56–5.53	—	—	— —	—	—	—

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; DM, diabetes mellitus; NFG, normal fasting glucose; NGT, normal glucose tolerance; NTN, normotension; Pre-DM, pre-diabetes; Pre-HTN, pre-hypertension. Multivariate-adjusted model was adjusted for age, gender, body mass index, waist to hip, smoking, hypercholesterolemia and education.

DM only among women.[22] In the current study, we extended our findings and showed that among different phenotypes of glucose tolerance status, the CVD risk of pre-HTN was found only among those with DM.

Unlike to the studies conducted among American and Chinese population,[17,18] we found a risk of about 50% for CVD events among the pre-DM population in the presence of BP < 120/80 mm Hg. Recent meta-analysis conducted by Xu *et al.*[12] showed that the risk of CHD was increased in participants with impaired fasting glucose tolerance defined by the American Diabetes Association or WHO criteria. On the other hand, among non-diabetic Turkish population, it was shown that the impact of impaired fasting glucose was modulated by the presence of metabolic syndrome;[23] on the other hand, impaired glucose tolerance alone, independently predicted CHD risk among women.[24] Data from 19 European cohorts including 12 566 men and 10 874 women with both FPG and 2 h-PCPG within the normoglycemic range showed high 2 h-PCPG was associated

increased CVD mortality.[25] In the current study, we defined pre-DM as impaired fasting glucose or impaired glucose tolerance, and did not stratify the pre-DM group, considering the limited number of events.

The current study extends findings of previous studies by showing all-cause mortality as the outcome of interest in which we observed increased risk in all of the individuals with HTN, regardless of glucose tolerance status. Although association of HTN with all-cause and CVD mortality is not a new finding,[26,27] our study clarifies that this association persists even in those with NGT. Furthermore, we showed that compared with NFG/NGT population, BP $<$ 120/80 mm Hg among diabetic individuals, not on antihypertensive medications, increased all-cause mortality risk by about 100%, although the diabetic population with pre-HTN had no significant risk. In line with our study, the recent Kailuan Study conducted among a Chinese diabetic population showed that baseline BP $<$ 120/80mm Hg was significantly associated with incident all-cause mortality but not with CVD, relative to BP of 120 to 139/80 to 89 mm Hg.[16] Table 1 shows that among the study population, NTN patients with type 2 DM are more likely to be male and smoker and have higher FPG but lower BMI, compared to the other groups. Furthermore, we showed that among the diabetic population, being male, having lower BMI or high FPG and being a smoker were independent risk factors for mortality events.[28] Moreover, diabetic patients may experience other diseases such as infection that result in impaired cardiac output and abnormal vasodilatation, showing a decrease in blood pressure.[29] Hence, as reported by WU Z *et al*., a relatively low BP may reveal the evolution toward complex diabetic comorbidities and mortality.[16] In the current study, we extend the results of WU Z *et al*. by showing a similar trend among a pre-DM population with BP $<$ 120/80, with increased risk of 48% for CVD, whereas the presence of pre-HTN with pre-DM was not associated with any risk.

Regarding the presence of both pre-DM and pre-HTN, the National Health and Nutrition Examination Survey found US adults showing this phenotype had a worse CVD risk profile,[30] with authors concluding that these populations are on an accelerated pathway to early CVD events. Despite the high prevalence and incidence of pre-HTN and pre-DM among Iranian populations,[4,5] however, we found no risk in our population with coexisting pre-HTN and pre-DM for CVD and mortality outcomes. Importantly, these findings should be interpreted with caution; in fact, the statistical power of study was 43% to detect HR of 1.27 of pre-HTN and pre-DM groups for CVD.

To mention the study limitations, first, as inherent in any prospective study, level of risk factors at the baseline examination might have changed during the follow-up period. As such, some degree of misclassification might have occurred, leading to biased estimated HRs toward the null. Second, our definitions for DM did not include HbA1c, so it is possible that some cases not diagnosed using FPG or 2 h-PCPG may have been missed. Third, we did not sex-stratify our data analysis considering the absence of interactions between gender and different categories of glucose tolerance and blood pressure for different outcomes, as shown in other studies.[17–19] Fourth, this study has been conducted on a sample of Iranian population living in Tehran and further studies should be conducted to determine whether our findings could be applicable to other populations. As strengths, this is among the first studies to examine the impact of different combinations of glycemic levels and BP status with all-cause mortality outcomes and the third one regarding CVD/CHD. Also, the length of follow-up and using actual measurements of variables and outcomes rather than self-reported data are other strengths of this study. Furthermore, we used both FPG and 2 h-PCPG to categorise our participants into the pre-DM and NGT groups.

To conclude, HTN caused significant increase in risk of CVD/CHD and all-cause mortality regardless of glucose tolerance status, indicating the importance of controlling HTN for CVD prevention even among NGT populations. Furthermore, we showed that blood pressure $<$ 120/80 mm Hg among pre-diabetic and diabetic populations, not on antihypertensive medications, was generally associated with worse health outcomes. And the last but not least, the presence of both pre-disease states was not associated with any risk for CVD/CHD or mortality. Considering the observational nature of this study, these findings should be confirmed in context of clinical trials for obtaining definite conclusion.

What is known about the topic?

- It is well-known that hypertension and diabetes have significant role in cardiovascular disease and all-cause mortality.

What this study adds?

- Hypertension is associated with increased risk of CVD and mortality events, regardless of glucose tolerance status.
- The presence of both pre-diabetes and pre-hypertension was not associated with any risk for CVD/CHD or mortality events.
- Blood pressure $<$ 120/80 mm Hg among pre-diabetic/diabetic population, not on antihypertensive medications, was generally associated with worse health outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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