Systolic blood pressure and all-cause mortality in normoglycemia, prediabetes, and diabetes

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Abstract

Background The optimal blood pressure (BP) level for diabetic patients remains controversial, and population-based evidence on BP management for individuals with normoglycemia and prediabetes is insufficient. We aimed to investigate the associations between systolic blood pressure (SBP) and all-cause mortality among US adults with different glucose metabolism.

Methods We used data from the 1999–2014 National Health and Nutrition Examination Survey (NHANES, n = 40,046) with comprehensive baseline examination and follow-up assessment. Restricted cubic spline was performed to examine dose-response relationship between continuous SBP and all-cause mortality. Cox regression models were used to estimate hazard ratios of all-cause mortality for SBP categories.

Results Over 32,5450 person-years of follow-up (median 8.1 years), 4745 all-cause death (11.8%) were recorded, corresponding to an event rate of 14.58 per 1000 patient years. U-shaped associations between SBP and all-cause mortality were observed regardless of glucose status. The lowest mortality risk of optimal SBP (mmHg) by group was 115–120 (normoglycemia), 120–130 (prediabetes), and 125–135 (diabetes). Compared with the reference group, SBP < 100 mmHg was significantly associated with 49% (HR = 1.49, 95%CI: 1.13–1.96), 57% (1.57, 1.07–2.3), and 59% (1.59, 1.12–2.25) higher mortality risk in normoglycemia, prediabetes, and diabetes, respectively. The multivariable-adjusted HRs of all-cause mortality for SBP of 150–159 mmHg and ≥ 160 mmHg were 1.35 (1.08–1.70) and 1.61 (1.31–1.98), 1.44 (1.13–1.83) and 1.66 (1.33–2.08), and 1.29 (1.02–1.65) and 1.37 (1.09–1.72), respectively.

Conclusions U-shaped relationships between SBP and all-cause mortality existed regardless of diabetes status. The optimal SBP range for the lowest mortality was gradually higher with worsening glucose status.

Background

Hypertension and abnormal glucose metabolism often coexist. Patients with established hypertension and diabetes mellitus (DM) have a 4-fold increased risk for the development of cardiovascular diseases (CVD) and substantially higher risk of CVD death and all-cause mortality [1, 2]. Whether prediabetes (Pre-DM) alone is associated with adverse cardiovascular outcomes remains a source of debate [3, 4], but findings from several longitudinal studies and meta-analyses have provided adequate evidence that patients with Pre-DM have 3–12 times higher risk of incident DM than in the general population [5–8]. Besides, coexistence with hypertension in prediabetic patients could accelerate the development of DM and further significantly increase CVD risk [3, 9, 10]. Considering the high prevalence of DM and Pre-DM and subsequent huge disease burden globally [1, 11, 12], especially accompanied with hypertension, blood pressure (BP) management in these large populations becomes particularly urgent.

However, data on targeting hypertension for reducing CVD risk has shown mixed results, especially in persons with DM [13, 14]. The discordant results of the recent Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial and the Systolic Blood Pressure Intervention Trial (SPRINT)
add to this uncertainty. ACCORD demonstrated a nonsignificant reduction in CVD events (except for stroke) with intensive systolic blood pressure (SBP) treatment (below 120 mmHg) compared with SBP below 140 mmHg over 5 years of follow-up in older adults in US with type 2 DM at high cardiovascular risk [15]. However, in SPRINT [16], CVD risk and all-cause mortality were substantially reduced with similar SBP treatment targets in high risk patients. Of note, participants with DM in SPRINT were excluded. Controversies becomes more intense when SBP below 120 mmHg was found to be associated with increased risk for cardiovascular death, total mortality in patients at high cardiovascular risk [17], as well as the results of J-shaped relationship between SBP and cardiovascular outcomes in patients with or without DM [18, 19]. Moreover, very few published data focused on the outcome benefit of the optimal SBP levels in patients with normoglycemia and Pre-DM, and the relationship between SBP and all-cause mortality in these individuals remains unclear [20, 21]. The current study, using data from the National Health and Nutrition Examination Surveys (NHANES), has allowed us to observe the association between SBP and all-cause mortality among individuals with normoglycemia, Pre-DM, and DM.

Methods

Study population

We analyzed data from successive NHANES over 15 years (1999–2004, 2005-10, and 2011-14) to examine the relationship between baseline SBP and mortality by glycemic status (ie, normoglycemia, Pre-DM and DM). Sample populations such that 2-years NHANES cycle was nationally representative of the US civilians who were not in an institution were recruited using a complex multistage sampling method. The US National Center for Health Statistics (NCHS) Research Ethics Review Board approved NHANES and all participants provided written informed consent before participation. Depending on previous publications, the response rates from 1999–2014 ranged from 75 to 80% [22]. More detailed descriptions of the survey design were released elsewhere [23–25]. Our analyses included all participants aged 18 and older with no self-reported diabetes whose blood samples were obtained after fasting for a minimum of 8 h for assessment and all participants with self-reported DM irrespective of fasting status. We excluded participants who had missing DM history, missing BP values, missing hemoglobin A1c (HbA1c) or fasting blood glucose (FBG), and missing mortality data. After implementing the exclusion criteria, there were 40,046 participants remained for data analysis (Fig. 1).

BP and Blood glucose Measurement

Two certified physicians and two health technologists were trained to collect NHANES BP data using approved protocols by the American Heart Association. Briefly, participants were rested upon arrival and BP was then measured with patient in the seated position using a mercury sphygmomanometer and an appropriately sized cuff. The average of three consecutive BPs measured during that visit was recorded as the baseline BP of that participant. Hypertension in our analysis was defined as the use of antihypertensive medications or a mean resting SBP at least 130 mmHg or diastolic blood pressure (DBP) at least 80 mmHg according to the latest guidelines [26].
FBG (mg/dL) and HbA1c (%) were estimated using standardized laboratory techniques. Diagnosed diabetes was defined as taking antihyperglycemic medications or having a positive response to the question: “Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?”. Undiagnosed diabetes was defined as an FPG of 126 mg/dL (7·0 mmol/L) or higher or a HbA1c of 6·5% (48 mmol/mol) or higher. Diabetic participants in our analysis were the combination of having diagnosed and undiagnosed diabetes. We classified prediabetes as an FPG of 100–125 mg/dL (5·6–6·9 mmol/L) or an HbA1c of 5·7–6·4% (39–47 mmol/mol), and normoglycemia as an FPG less than 100 mg/dL (5·6 mmol/L) and HbA1c less than 5·7% (39 mmol/mol) [27].

**Study End Points**

Our outcome was all-cause mortality, which were obtained in the National death Index (NDI), a centralized database of US death records gathered from National Center for Health Statistics (NCHS). Mortality status was ascertained through probabilistic record matching with the NDI [28]. Participants were followed up until the intended outcome or the end of the study (December 2015), whichever came first.

**Other Variables of Interest**

Age, sex, ethnicity, smoking status, educational level, history of hypertension, CVD (any prior diagnosed congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack or stroke), and cancer were self-reported by questionnaire during the interview. Smoking status, baseline hypertension, CVD and cancer history were categorized into yes or no. Education level was categorized into less than or more than high school. Medication usage including antihypertensive drugs, antihyperglycemic drugs, antiplatelet drugs, and insulin were obtained from self-report and prescription medications questions. Anthropometric indicators including height, weight, DBP, and body mass index (BMI, calculated by weight divided by height squared [kg/m²]) and laboratory examination including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and estimated glomerular filtration rate (eGFR, calculated using Modification of Diet in Renal Disease formula [29]) were conducted at NHANES mobile examination centers. Dietary energy was assessed using dietary recall. Detailed examination methods and questionnaire information can be referred to https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

**Statistical Analysis**

For each glycemic group (normoglycemia, Pre-DM and DM), we reported sociodemographic and clinical characteristics and compared the differences between groups using the One-Way ANOVA, Kruskal-Wallis H test and chi-square tests. Data were presented as mean standard deviation (SD) for continuous variables and percentage for categorical variables, as appropriate. Kaplan–Meier curves were first used to compare the event-free survival of diabetes status with and without hypertension. The survival curves were then compared between SBP categories using Log-rank test. Thereafter, the shapes of the associations between SBP and all-cause mortality in participants with normoglycemia, Pre-DM, and DM were investigated. We utilized adjusted restricted cubic splines to develop a hazard ratio (HR) curve to
examine full-range associations of SBP with mortality risk to test whether there was a dose-response or non-linear association of SBP as a continuous variable. Three knots at quartiles 25th, 50th, and 75th were chosen. Variables adjusted in the cubic spline analysis were described below. Next, Cox proportional hazards models were used to estimate HR with 95% confidence interval (CI) of all-cause mortality for SBP as continuous variable (per SD change) or as categories (<100, 100–109, 110–119 (reference), 120–129, 130–139, 140–149, 150–159, and ≥160 mmHg). Crude associations between SBP and mortality with and without adjustment for potential confounders were examined in different models. Adjusted models incorporated covariates including DBP, age, gender, race, education, smoking status, BMI, baseline CVD, baseline cancer, baseline hypertension, dietary intake, TC, HDL-C, eGFR, statin, antiplatelet drugs, antidiabetic drugs, and antihypertensive medications. The Cox proportional hazard analysis was stratified by glycemic status. All statistical tests were two-sided, with \( P < 0.05 \) considered significant. All statistical analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Baseline characteristics of study participants**

Of 40,046 participants, 57.9% (n=23,176) had normoglycemia, 26.7% (n=10,685) had prediabetes and 15.4% (n=6185) had diabetes. Demographic, clinical and laboratory data at baseline of study participants according to glucose status were provided in Table 1. Overall, 48.7% were male and the mean age was 47.2 years (SD=19.4). The average of baseline SBP was 119 mmHg (SD=17.4) in normoglycemia, 128 mmHg (SD=19.7) in Pre-DM and 132mmHg (SD=20.7) in DM. The overall mortality was 7.8% (n=1818) in participants with normoglycemia, 14.2% (n=1514) in those with Pre-DM, and 22.8% (n=1413) in those with DM. Significant differences between groups were found in all covariates at baseline.

Figure 2 showed the all-cause event-free survival stratified by hypertension status in three glycemic groups. DM had lower all-cause event-free survival compared with Pre-DM, which was lower than normoglycemia. Hypertension was associated with a reduced mortality event-free survival regardless of diabetes status (Log rank \( P <0.0001 \)). In addition, significant differences in survival of all-cause mortality were observed among the SBP groups in all three glycemic groups (Figure 3).

**Natures of associations of systolic blood pressure levels with mortality risk**

In the full multivariable models of the restricted cubic splines treating SBP as a continuous variable, the relations of SBP and all-cause mortality risk were both U-shaped in participants with normoglycemia, Pre-DM and DM. The lowest risk was observed at SBP between 115 and 120 mmHg in normoglycemia, 120 and 130 mmHg in Pre-DM and 125 and 135 mmHg in DM (Figure 4).
Over 32,5450 person-years of follow-up (median 8.1 years), 4745 all-cause death (11.8%) were recorded, corresponding to an event rate of 14.58 per 1000 patient years in the study population. Higher SBP levels were significantly associated with increased risk of all-cause mortality; per SD increase in SBP associated with a 12%, 11%, and 8% higher mortality in normoglycemia, Pre-DM, and DM, respectively (Table 2).

In normoglycemic participants, the multivariable-adjusted HRs of all-cause mortality for SBP group of <100, 100-109, 110-119 (reference), 120-129, 130-139, 140-149, 150-159, and ≥160 mmHg were 1.49 (95%CI: 1.13-1.96), 1.00 (0.89-1.35), 1.00 (0.92-1.30), 1.17 (0.96-1.42), 1.12 (0.91-1.39), 1.35 (1.08-1.70), and 1.61 (1.32-1.98), respectively. In prediabetic participants, the HRs of all-cause mortality for SBP groups were 1.57 (95%CI: 1.07-2.3), 1.31 (1.01-1.71), 1.00, 1.19 (0.96,1.46), 1.16 (0.93-1.44), 1.25 (0.99-1.57), 1.44 (1.13-1.83), and 1.66 (1.33-2.08), respectively. Among patients with diabetes, the values were 1.59 (1.12,2.25), 1.04 (0.77,1.4), 1.00, 1.18 (0.95,1.45), 1.06 (0.85,1.31), 1.08 (0.86,1.35), 1.29 (1.02,1.65), and 1.37 (1.09,1.72), respectively. Both higher (≥150 mmHg) and lower (<100 mmHg) were significantly associated with greater risk of all-cause mortality in all subpopulations. Besides, SBP of 100-109 mmHg associated with increased all-cause mortality in prediabetic individuals (Table 3).

**Discussion**

In this population-based cohort study among US adults with different glucose metabolism, we assessed the associations of SBP levels and risk of all-cause mortality in individuals with normoglycemia, Pre-DM, and DM. A U-shaped relationship between SBP and all-cause mortality was observed regardless of glycemic status. The lowest risk was observed at SBP between 115 and 120 mmHg in normoglycemia, 120 and 130 mmHg in Pre-DM and 125 and 135 mmHg in DM, with both lower (<100 mmHg) or higher SBP (≥150 mmHg) were significantly associated with increased mortality risk. The optimal SBP range for the lowest mortality was gradually higher with worsening glucose status.

The optimal BP target for diabetic patients remains controversial for the past few decades. Findings from several meta-analyses of BP lowering trials found that intensive treatment in diabetic patients can effectively reduce the risk of CVD and all-cause mortality. A recent network meta-analysis of 42 antihypertensive trials including 144,220 patients found that subjects who achieved SBP at 120–124 mmHg significantly reduced risk of CVD events compared with higher achieved BP levels [30]. In another meta-analysis of BP-lowering trials including 613,815 patients with DM, per 10 mmHg decreased SBP was associated with 12% lower CVD risk. Benefits of reduced CVD and all-cause mortality persisted to SBP <130 mmHg [13]. In contrast, another meta-analysis (n = 73,738) found that effects of antihypertensive treatment in diabetic patients were attenuated when SBP was 130 mmHg or lower [31]. Our study also demonstrated that higher SBP levels were associated with increased risk of all-cause mortality and the benefits was attenuated when SBP lower than 125 mmHg in patients with DM.

The U-shaped association between SBP and mortality risk in diabetic patients were also demonstrated in previous studies. Data from the LSU Health Care Services Division (LSUHCSD) study of 35,261 patients with type 2 diabetes showed a U-shaped relationship between SBP and all-cause mortality, which was in
consistent with our findings [32]. However, the LSUHCSD study suggested maintaining SBP at 130–150 mmHg, with SBP < 120 mmHg and ≥ 160 mmHg both associated with increased risk of all-cause death. Relatively, our study suggested a narrower and lower range because the lowest risk of all-cause mortality was observed at SBP 125–135 mmHg in patients with DM in the present study. Similar associations between SBP and all-cause mortality (U-shaped) in diabetic patients were also confirmed in the Swedish National Diabetes Register studies [33, 34], which were different from previous widely published J-shaped association between BP and CVD outcomes among patients with diabetes [35].

The recently published SPRINT results showed that in high-risk populations without DM, intensive BP reduction below 120 mmHg can significantly improve cardiovascular prognosis [16]. However, the results of ACCORD failed to achieve the beneficial effect of strengthening BP in the diabetic population at high cardiovascular risk [15]. These inconsistent results further increased the controversy regarding the optimal BP target of in people with diabetes or without diabetes [36]. In addition, it is worth considering that in non-diabetic patients, considering the harm of microvascular or macrovascular damages that have been proven to have higher blood glucose levels such as prediabetes [37], especially combined with hypertension, the appropriate BP target among these people still needs to be better discussed.

To the best of our knowledge, the current study for the first time found a U-shaped association between SBP and all-cause mortality among normoglycemic and prediabetic populations. It was estimated that by 2011–2014, 78·5 million adults in US had prediabetes and more than a third of those had hypertension [22]. Identifying prediabetes and addressing related cardiovascular risk factors such as hypertension is important and urgent to reduce cardiovascular and renal burdens, which was recommended by recent modifications to the US Preventive Services Task Force diabetes screening guideline [38]. However, few studies focused on the BP management in normoglycemia and Pre-DM [20, 21]. A post hoc analysis of SPRINT demonstrated that the beneficial effects of intensive treatment extend to those with Pre-DM and fasting normoglycemia [21]. Lowering SBP to below 120 mmHg was associated with a 23% decreased risk of all-cause mortality and 31% decreased risk of primary outcome among those with Pre-DM in SPRINT. Importantly, there was no attenuation of benefits between participants with Pre-DM and those with normoglycemia. However, although SPRINT excluded participants with DM, the population enrolled for analysis are at high cardiovascular risk [16]. It is unclear whether prediabetic individuals in general could benefit from intensive BP lowering (< 120 mmHg). According to a previous study, only less than one-third of US adults with hypertension were eligible for clinical trial and there was a large gap of evidence concerning benefits of intensive treatment for younger adults at lower cardiovascular risk of older adults with multimorbidity [39]. Our results expanded evidence that lowering SBP to less than 100 mmHg was significantly associated with higher all-cause mortality risk among US adults with Pre-DM or normoglycemia. One explanation of higher mortality associated with lower SBP levels in normoglycemic individuals was that intensive SBP reduction could accelerate the development of DM and thus may worsen cardiovascular outcomes in this population [40]. Besides, strict BP control could increase CVD and mortality through the under-perfusion of vital organs [41]. Further investigation is warrant to clarify the underling mechanism among normoglycemic and prediabetic individuals.
Moreover, in a Chinese cohort, Tian et.al demonstrated that BP of 130–139/80–89 mmHg was associated with increased risk of CVD events in Chinese adults with DM, but not in those with Pre-DM or normoglycemia [20]. The current study also suggested that SBP of 130–139 mmHg had no significant association with all-cause mortality compared with SBP of 110–119 mmHg. In addition, our study expanded evidence on the BP management for normoglycemic and prediabetic individuals, suggesting that both lower and higher SBP levels associated with higher all-cause mortality. However, more large-scale and randomized trials are needed to better determine the optimal range of blood pressure management in these populations.

The present study has several strengths. Nationally representative data from the NHANES collected by standardized protocols were employed in our study and for that reason, the findings could be generalized to a broader population. In addition, we were able to adjust numerous potential confounding factors due to the comprehensive information about demographic features, socioeconomic status, lifestyle factors and anthropometric measures included in the NHANES. Despite those advantages, some limitations should be taken into consideration in interpreting our results. First, FBG and HbA1c were measured only once at baseline, and there was absence of postprandial blood glucose after 2 hours, which may lead to a bias in the estimate of the total number of diabetes. Furthermore, the number of prediabetes in our study population might be underestimated because data of glucose tolerance were missing in NHANES. Second, our findings of the non-linear association between SBP and mortality risk do not imply causality because of the observational nature of the study. Presented SBP levels corresponding to the lowest risk of mortality in our study are also not a recommendation for an optimal treatment goal for prevention guidelines. Third, baseline factors such as BP levels, lipids, and drug treatment may change during the follow-up period, which may result in misclassification and bias estimated HR. Of note, the proportion of participants that progressed from prediabetes to diabetes was not assessed due to the cross-sectional nature of NHANES. Finally, although we adjusted for many plausible confounders, residual or unmeasured confounding may exist.

**Conclusion**

In conclusion, the association of SBP with all-cause mortality was U-shaped regardless of diabetes status. Both lower (<100 mmHg) and higher (≥150 mmHg) SBP were associated with greater risk of all-cause mortality. The optimal SBP range for the lowest mortality was gradually higher with worsening glucose status. Of note, there is little or insufficient evidence on the outcome benefit of BP lowering treatment among adults with Pre-DM, and more well-designed, large scale studies are needed in the future to reduce the heavy disease burden in this growing population.

**Abbreviations**

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; FBG, fasting blood glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride;
LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease.

Declarations

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Authors’ contributions

C-CL and L-L analyzed the data and drafted the manuscript. Y-QF and Y-QH designed the study, interpreted the data and contributed to critically revising the manuscript. J-YH, Y-LY, and KL helped manuscript editing and data analysis. Y-QF is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Availability of data and materials

Detailed examination methods, questionnaire information, and mortality data can be referred to https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.
Ethics approval and consent to participate

Our study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of the Centers for Disease Control and Prevention. All participants gave written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to declare.

References

1. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA, et al. 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(9785):31-40.

2. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993;16(2):434-44.

3. Hubbard D, Colantonio LD, Tanner RM, Carson AP, Sahujuja S, Jaeger BC, Carey RM, Cohen LP, Shimbo D, Butler M, et al. Prediabetes and Risk for Cardiovascular Disease by Hypertension Status in Black Adults: The Jackson Heart Study. Diabetes Care. 2019;42(12):2322-29.

4. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. Bmj. 2016;355i5953.

5. Morris DH, Khunti K, Achana F, Srinivasan B, Gray LJ, Davies MJ, Webb D. Progression rates from HbA1c 6.0-6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis. Diabetologia. 2013;56(7):1489-93.

6. Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, Yazdi H, Booker L. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes Res Clin Pract. 2007;78(3):305-12.

7. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.
8. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344(18):1343-50.

9. Liu HH, Cao YX, Li S, Guo YL, Zhu CG, Wu NQ, Gao Y, Dong QT, Zhao X, Zhang Y, et al. Impacts of Prediabetes Mellitus Alone or Plus Hypertension on the Coronary Severity and Cardiovascular Outcomes. Hypertension. 2018;71(6):1039-46.

10. Qiu M, Shen W, Song X, Ju L, Tong W, Wang H, Zheng S, Jin Y, Wu Y, Wang W, et al. Effects of prediabetes mellitus alone or plus hypertension on subsequent occurrence of cardiovascular disease and diabetes mellitus: longitudinal study. Hypertension. 2015;65(3):525-30.

11. 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. 2017;34(1):69-78.

12. Bullard KM, Saydah SH, Imperatore G, Cowie CC, Gregg EW, Geiss LS, Cheng YJ, Rolka DB, Williams DE, Caspersen CJ. Secular changes in U.S. Prediabetes prevalence defined by hemoglobin A1c and fasting plasma glucose: National Health and Nutrition Examination Surveys, 1999-2010. Diabetes Care. 2013;36(8):2286-93.

13. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957-67.

14. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, Pepine CJ. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. Jama. 2010;304(1):61-8.

15. Cushman WC, Evans GW, Byington RP, Goff DC, Jr., Grimm RH, Jr., Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1575-85.

16. Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015;373(22):2103-16.

17. Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC, Tendera M, Tavazzi L, Bhatt DL, Steg PG. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet. 2016;388(10056):2142-52.

18. Reboldi G, Gentile G, Angeli F, Ambrosio G, Mancia G, Verdecchia P. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. J Hypertens. 2011;29(7):1253-69.

19. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-
analyses of randomized trials. Circulation. 2011;123(24):2799-810, 9 p following 810.
20. Tian J, Sheng CS, Sun W, Song X, Wang H, Li Q, Li W, Wang W. Effects of High Blood Pressure on Cardiovascular Disease Events Among Chinese Adults With Different Glucose Metabolism. Diabetes Care. 2018;41(9):1895-900.
21. Bress AP, King JB, Kreider KE, Beddhu S, Simmons DL, Cheung AK, Zhang Y, Doumas M, Nord J, Sweeney ME, et al. Effect of Intensive Versus Standard Blood Pressure Treatment According to Baseline Prediabetes Status: A Post Hoc Analysis of a Randomized Trial. Diabetes Care. 2017;40(10):1401-8.
22. Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988-2014. Lancet Diabetes Endocrinol. 2018;6(5):392-403.
23. Bao W, Liu B, Simonsen DW, Lehmler HJ. Association Between Exposure to Pyrethroid Insecticides and Risk of All-Cause and Cause-Specific Mortality in the General US Adult Population. JAMA Intern Med. 2019;180(3):367-74.
24. Palta P, Huang ES, Kalyani RR, Golden SH, Yeh HC. Hemoglobin A(1c) and Mortality in Older Adults With and Without Diabetes: Results From the National Health and Nutrition Examination Surveys (1988-2011). Diabetes Care. 2017;40(4):453-60.
25. Fain JA. NHANES. Diabetes Educ. 2017;43(2):151.
26. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19):e127-e248.
27. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S14-S31.
28. National Center for Health Statistics. 2011 Public-Use Linked Mortality Files. Available from: https://www.cdc.gov/nchs/data/datalinkage/2011_linked_mortality_file_matching_methodology.pdf. Accessed December 20, 2019.
29. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1-266.
30. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, He H, Chen J, Whelton PK, He J. Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis. JAMA Cardiol. 2017;2(7):775-81.
31. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. Bmj. 2016;352i717.
32. Li W, Katzmarzyk PT, Horswell R, Wang Y, Johnson J, Hu G. Blood pressure and all-cause mortality among patients with type 2 diabetes. Int J Cardiol. 2016;206116-21.
33. Adamsson Eryd S, Gudbjörnsdottir S, Manhem K, Rosengren A, Svensson AM, Miftaraj M, Franzén S, Björck S. Blood pressure and complications in individuals with type 2 diabetes and no previous cardiovascular disease: national population based cohort study. Bmj. 2016;354i4070.

34. Sundström J, Sheikhi R, Ostgren CJ, Svennblad B, Bodegård J, Nilsson PM, Johansson G. Blood pressure levels and risk of cardiovascular events and mortality in type-2 diabetes: cohort study of 34 009 primary care patients. J Hypertens. 2013;31(8):1603-10.

35. Banach M, Aronow WS. Blood pressure j-curve: current concepts. Curr Hypertens Rep. 2012;14(6):556-66.

36. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. J Hypertens. 2017;35(5):922-44.

37. Emanuelsson F, Marott S, Tybjærg-Hansen A, Nordestgaard BG, Benn M. Impact of Glucose Level on Micro- and Macrovascular Disease in the General Population: A Mendelian Randomization Study. Diabetes Care. 2020;43(4):894-902.

38. Siu AL. Screening for Abnormal Blood Glucose and Type 2 Diabetes Mellitus: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2015;163(11):861-8.

39. Anderson TS, Odden M, Penko J, Kazi DS, Bellows BK, Bibbins-Domingo K. Generalizability of Clinical Trials Supporting the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline. JAMA Intern Med. 2020.

40. Roumie CL, Hung AM, Russell GB, Basile J, Kreider KE, Nord J, Ramsey TM, Rastogi A, Sweeney ME, Tamariz L, et al. Blood Pressure Control and the Association With Diabetes Mellitus Incidence: Results From SPRINT Randomized Trial. Hypertension. 2020;75(2):331-38.

41. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, Cifkova R, Clément D, Coca A, Dominiczak A, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens. 2009;27(11):2121-58.

Tables

Table 1 Baseline characteristics of study participants according to glucose status
|                      | Overall (n=40046) | Normoglycemia (n=23176) | Prediabetes (n=10685) | Diabetes mellitus (n=6185) | P-value       |
|----------------------|-------------------|-------------------------|-----------------------|---------------------------|--------------|
| **Age**              |                   |                         |                       |                           | <0.001       |
| Gender               |                   |                         |                       |                           | <0.001       |
| Male                 | 19484 (48.7%)     | 10610 (45.8%)           | 5694 (53.3%)          | 3180 (51.4%)              |              |
| Female               | 20562 (51.3%)     | 12566 (54.2%)           | 4991 (46.7%)          | 3005 (48.6%)              |              |
| **Race**             |                   |                         |                       |                           |              |
| Non-White            | 21486 (53.7%)     | 11883 (51.3%)           | 5828 (54.5%)          | 3775 (61.0%)              |              |
| White                | 18560 (46.3%)     | 11293 (48.7%)           | 4857 (45.5%)          | 2410 (39.0%)              |              |
| **Smoker**           |                   |                         |                       |                           |              |
| Less than high school| 10390 (25.9%)     | 4812 (20.8%)            | 3152 (29.5%)          | 2426 (39.2%)              | <0.001       |
| Follow-up time       | 97.5 ± 54.1       | 107 ± 54.9              | 85.7 ± 50.1           | 81.7 ± 49.3               | <0.001       |
| **BMI**              | 28.5 ± 6.58       | 27.1 ± 5.90             | 29.7 ± 6.72           | 31.8 ± 7.18               | <0.001       |
| **SBP**              | 124 ± 19.3        | 119 ± 17.4              | 128 ± 19.7            | 132 ± 20.7                | <0.001       |
| **DBP**              | 69.4 ± 13.5       | 69.0 ± 12.6             | 70.8 ± 14.0           | 68.3 ± 15.4               | <0.001       |
| **FBG**              | 99.9 ± 37.1       | 85.8 ± 7.89             | 100 ± 11.0            | 152 ± 70.6                | <0.001       |
| **HbA1c**            | 5.64 ± 1.03       | 5.19 ± 0.286            | 5.69 ± 0.351          | 7.20 ± 1.78               | <0.001       |
| **TC**               | 196 ± 42.9        | 193 ± 41.6              | 202 ± 42.0            | 193 ± 48.0                | <0.001       |
| **TG**               | 136 ± 119         | 121 ± 98.4              | 144 ± 105             | 181 ± 185                 | <0.001       |
| **LDLC**             | 115 ± 35.9        | 113 ± 35.1              | 122 ± 36.1            | 108 ± 36.8                | <0.001       |
| **HDLC**             | 52.8 ± 15.8       | 54.7 ± 16.0             | 51.3 ± 15.5           | 48.0 ± 14.2               | <0.001       |
| **eGFR**             | 90.1 ± 30.2       | 96.0 ± 31.1             | 83.3 ± 24.8           | 79.9 ± 30.1               | <0.001       |
| Energy intake        | 2140 ± 1020       | 2240 ± 1070             | 2080 ± 966            | 1860 ± 890                | <0.001       |
| Cancer at baseline   | 3309 (8.3%)       | 1341 (5.8%)             | 1161 (10.9%)          | 807 (13.0%)               | <0.001       |
| CVD at baseline      | 4044 (10.1%)      | 1209 (5.2%)             | 1308 (12.2%)          | 1527 (24.7%)              | <0.001       |
| Hypertension at baseline | 21017 (52.5%) | 8931 (38.5%)             | 6958 (65.1%)          | 5128 (82.9%)              | <0.001       |
| Statin               | 4869 (12.2%)      | 1227 (5.3%)             | 1647 (15.4%)          | 1995 (32.3%)              | <0.001       |
| Antiplatelet drugs   | 731 (1.8%)        | 165 (0.7%)              | 237 (2.2%)            | 329 (5.3%)                | <0.001       |
| Insulin              | 913 (2.3%)        | 0 (0%)                  | 0 (0%)                | 913 (14.8%)               | <0.001       |
| Antidiabetic drugs   | 2860 (7.1%)       | 0 (0%)                  | 0 (0%)                | 2860 (46.2%)              | <0.001       |
| Antihypertensive drugs | 10152 (25.4%)  | 2989 (12.9%)             | 3586 (33.6%)          | 3577 (57.8%)              | <0.001       |
| All-cause mortality  | 4745 (11.8%)      | 1818 (7.8%)             | 1514 (14.2%)          | 1413 (22.8%)              | <0.001       |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease.

Table 2 Hazard ratios for all-cause mortality according to systolic blood pressure categories among individuals with prediabetes or diabetes.
| SBP (mmHg) | n/total | Event rate/1000 person-years | Unadjusted HR (95% CI) | Adjusted HR (95% CI) |
|-----------|---------|-------------------------------|------------------------|----------------------|
| **Normoglycemia**<sup>a</sup> |         |                               |                        |                      |
| per SD change |         |                               |                        |                      |
| <100        | 78/1822 | 4.76                          | 1.94 (1.88,2.01) *     | 1.12 (1.06,1.18) *   |
| 100-109     | 178/5339| 3.73                          | 1.04 (0.81,1.34) *     | 1.49 (1.13,1.96) *   |
| 110-119     | 279/6775| 4.58                          | 0.81 (0.67,0.98) *     | 1.09 (0.89,1.35)     |
| 120-129     | 319/4408| 8.02                          | 1.75 (1.49,2.06) *     | 1.09 (0.92,1.30)     |
| 130-139     | 292/2294| 14.30                         | 3.13 (2.66,3.69) *     | 1.17 (0.96,1.42)     |
| 140-149     | 199/1184| 19.22                         | 4.23 (3.52,5.07) *     | 1.12 (0.91,1.39)     |
| 150-159     | 173/614 | 33.80                         | 7.53 (6.23,9.1) *      | 1.35 (1.08,1.70) *   |
| ≥160        | 300/740 | 47.87                         | 10.64 (9.04,12.52) *   | 1.61 (1.32,1.98) *   |
| **Prediabetes**<sup>a</sup> |         |                               |                        |                      |
| per SD change |         |                               |                        |                      |
| <100        | 39/339  | 17.13                         | 1.6 (1.13,2.26) *      | 1.57 (1.07,2.3) *    |
| 100-109     | 97/1195 | 11.78                         | 1.09 (0.85,1.4)        | 1.31 (1.01,1.71) *   |
| 110-119     | 182/2392| 10.84                         | 1.00                   | 1.00                 |
| 120-129     | 276/2469| 15.98                         | 1.47 (1.22,1.78) *     | 1.19 (0.96,1.46)     |
| 130-139     | 276/1832| 20.40                         | 1.85 (1.54,2.24) *     | 1.16 (0.93,1.44)     |
| 140-149     | 200/1060| 25.94                         | 2.37 (1.94,2.9) *      | 1.25 (0.99,1.57)     |
| 150-159     | 173/644 | 35.21                         | 3.18 (2.58,3.91) *     | 1.44 (1.13,1.83) *   |
| ≥160        | 271/754 | 48.45                         | 4.4 (3.65,5.31) *      | 1.66 (1.33,2.08) *   |
| **Diabetes**<sup>b</sup> |         |                               |                        |                      |
| per SD change |         |                               |                        |                      |
| <100        | 52/175  | 47.95                         | 2.22 (1.63,3.03) *     | 1.59 (1.12,2.25) *   |
| 100-109     | 73/494  | 21.74                         | 0.99 (0.75,1.3)        | 1.04 (0.77,1.4)      |
| 110-119     | 168/1119| 22.09                         | 1.00                   | 1.00                 |
| 120-129     | 245/1319| 27.71                         | 1.26 (1.03,1.53) *     | 1.18 (0.95,1.45)     |
| 130-139     | 273/1191| 33.27                         | 1.49 (1.23,1.81) *     | 1.06 (0.85,1.31)     |
| 140-149     | 198/772 | 36.39                         | 1.64 (1.33,2.01) *     | 1.08 (0.86,1.35)     |
| 150-159     | 158/487 | 47.35                         | 2.14 (1.72,2.66) *     | 1.29 (1.02,1.65) *   |
| ≥160        | 246/628 | 57.93                         | 2.61 (2.15,3.18) *     | 1.37 (1.09,1.72) *   |

SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval; *P<0.05

<sup>a</sup> Adjusted for age, sex, race, education, smoke, body mass index, diastolic blood pressure, baseline cardiovascular disease, baseline cancer, baseline hypertension, dietary intake, total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, statin, antiplatelet drugs, and antihypertensive drugs.

<sup>b</sup> Adjusted for age, sex, race, education, smoke, body mass index, diastolic blood pressure, baseline cardiovascular disease, baseline cancer, baseline hypertension, dietary intake, total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, statin, antiplatelet drugs, antihypertensive drugs, and antihyperglycemic drugs.

**Figures**
Figure 1

Flow chart of study participants. NHANES, National Health and Nutrition Examination Survey; HbA1c, hemoglobin A1c.
Figure 2

Kaplan–Meier curves of the event-free survival for all-cause mortality in persons with normoglycemia, prediabetes, and diabetes stratified by hypertension status.
Figure 3

Kaplan–Meier curves of the event-free survival for all-cause mortality according to SBP categories in (A) normoglycemia, (B) prediabetes, and (C) diabetes.
Figure 4

Adjusted cubic spline model of the association between hazard ratio of all-cause mortality and SBP of participants overall (A) and in normoglycemia (B), prediabetes (C) and diabetes (D). Models were adjusted for age, sex, race, education, smoke, body mass index, diastolic blood pressure, baseline cardiovascular disease, baseline cancer, baseline hypertension, dietary intake, total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, statin and antiplatelet drugs in normoglycemia and prediabetes, and additionally adjusted for antihypertensive drugs in diabetes.