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High pulse pressure is related to risk of type 2 diabetes mellitus in Chinese middle-aged females

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ABSTRACT

Background: To examine the association of risk of incident type 2 diabetes mellitus (T2DM) with high pulse pressure (PP) by sex.
Methods: We performed a prospective cohort study of 12,272 eligible participants (4664 males and 7608 females) without diabetes at baseline. Participants were classified as having normal PP (20–60 mm Hg) and high PP (>60 mm Hg) at baseline. The analysis was further stratified by sex, quartiles of age and high PP categories.
Results: During 6 years of follow-up, T2DM developed in 775 participants and the incidence was 10.57/1000 person-years. With PP 70 to 76 mm Hg, the multivariable adjusted hazard ratio (HR) (95% confidence interval) for incident T2DM in females was 1.722 (1.093–2.714) after adjustment for baseline age, smoking, alcohol intake, physical activity level and family history of T2DM, and 1.634 (1.037–2.575) after adjustment for the above factors and body mass index, waist circumference, blood lipid levels and fasting plasma glucose (FPG) category. After stratification by quartiles of age, for females aged 52 to 59, the multivariable adjusted HRs (95% CI) for high PP as compared to normal PP were 2.263 (1.517–3.377) and 2.140 (1.426–3.210) in different models. During follow-up, levels of FPG, fasting plasma insulin and homeostatic model assessment of insulin resistance index (HOMA-IR) were higher in females with higher than normal PP group, but β-cell function was impaired in the high PP group ($P < 0.05$).
Conclusion: High PP may be related to incident T2DM among female in China, especially women 52 to 59 years old.

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1. Introduction

With the improvement in living standards in China, the change in lifestyle and population aging, the prevalence of type 2 diabetes mellitus (T2DM) continues to increase. Moreover, diabetes and its complications have brought serious economic burden to society and families. Therefore, the prevention of diabetes has become a major public health concern in China.

Pulse pressure (PP) is a surrogate measure of arterial stiffness and a strong predictor of cardiovascular events in patients with T2DM [1]. T2DM has been associated with increased arterial stiffness [2]. PP may be increased in patients with diabetes because of arterial stiffness, but the conclusions of some studies exploring the direct risk of T2DM with high PP were controversial. Janghorbani et al. and Liu et al. found that PP was not a predictor of diabetes in non-diabetic first-degree relatives of patients with T2DM and in middle-aged people from the community [3,4], but Yasuno et al. found PP an independent predictor of new-onset diabetes in high-risk Japanese hypertensive patients [5].

Here, we used a large population-based cohort to explore the association between high PP and incidence of T2DM by sex.

2. Materials and methods

2.1. Study design and population

The cohort was established between July to August 2007 and July to August 2008. Overall, 20,194 participants were selected by cluster sampling method from a rural area of the Henan province. Subjects were ≥18 years old and of northern Chinese ancestry. A standard questionnaire was used to assess demographic characteristics, medical history, smoking and alcohol intake status, physical activity level, family history of T2DM and other risk factors. A total of 17,265 participants completed the follow-up from July to August 2013 and July to October 2014. The response rate was 85.5%. We excluded people with T2DM (n = 1302), type 1 DM (n = 13) and no fasting plasma glucose (FPG) data (n = 9) at baseline as well as those who died (n = 1110) or had missing biochemical

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data (n = 2555) during follow-up. We also excluded participants with PP <20 mm Hg (n = 4) at baseline. Therefore, we analyzed data for 12,272 eligible participants (4664 males and 7608 females). All participants signed an informed consent before entering the study. The study was approved by the Ethics Committee of Shenzhen University.

2.2. T2DM ascertainment

T2DM was defined as FPG ≥ 7.0 mmol/L or the use of insulin or oral hypoglycemic agents, and/or a self-reported history of T2DM [6].

2.3. Covariate measurement

Height, weight and waist circumference (WC) were measured in duplicate by using standard methods. Systolic and diastolic blood pressures were measured in triplicate at 30-s intervals, and the mean was used for analysis. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Overnight fasting blood samples were collected for measuring plasma glucose, total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C). Plasma glucose was measured by an oxidase enzymatic method. TC, TG and HDL-C were measured by using an automatic biochemical analyzer (Hitachi Inc., Tokyo). Low-density lipoprotein cholesterol (LDL-C) level was calculated by the Friedewald formula [7]. During follow-up, in addition to the above indicators, fasting plasma insulin (FPI) level was measured by use of a radioimmunoassay kit (Biotechnology Research Institute of North China, Beijing). Insulin resistance and β-cell function were calculated from FPG and insulin data by the homeostasis model assessment of insulin resistance (HOMA-IR index) [8].

Current smokers were defined as those who had smoked at least 100 cigarettes and still smoked during follow-up [9]. Alcohol drinkers were defined as those who had consumed 100 mL liquor in 30 days. Physical activity level for each individual was classified as low, moderate or high based on the International Physical Activity Questionnaire (IPAQ) [www.ipaq.ki.se]. PP was calculated as SBP minus DBP. High PP was defined as >60 mm Hg, low PP as <20 mm Hg and normal range PP from 20 to 60 mm Hg according to the Chinese Hypertension Prevention Guide [10]. Low weight was defined as BMI <18.5 kg/m^2, normal weight 18.5 to 23.9 kg/m^2, overweight 24 to 27.9 kg/m^2 and general obesity BMI ≥ 28 kg/m^2 [11]. WC ≥90 cm in men or ≥80 cm in women was classified as abdominal obesity [12]. Dyslipidemia was defined as the TC level ≥ 240 mg/dL and/or TG level ≥ 200 mg/dL and/or HDL-C level < 40 mg/dL and/or LDL-C level ≥ 160 mg/dL [13]. Impaired fasting glucose was defined as FPG 6.1 to 7.0 mmol/L [6].

2.4. Statistical analysis

The baseline data are summarized as median (interquartile range) for quantitative variables and number (percentage) for categorical variables. Differences in baseline characteristics between participants with and without T2DM were tested by nonparametric Wilcoxon test for quantitative variables and chi-square test for categorical variables. Cox proportional-hazards regression models were used to calculate the hazard ratio (HR) and corresponding 95% confidence interval (CI) for T2DM adjusted for potential risk factors of T2DM with 2 models: adjustment for (1) baseline age, smoking, alcohol intake, physical activity level and family history of T2DM and (2) the above factors plus BMI category (normal weight = 0, low weight = 1, overweight = 2, obesity = 3), WC category (normal weight = 0, obesity = 1), blood lipid category (normal lipidemia = 0, dyslipidemia = 1) and FPG category (normal FPG = 0, impaired fasting glucose = 1). Participants with normal PP at baseline were the reference group. $P < 0.05$ was considered statistically significant. Statistical analyses involved the use of SAS 9.1.3 (SAS Inst., Cary, NC, USA).

3. Results

3.1. Baseline characteristics of the study participants

During a median follow-up of 6 years, T2DM developed in 775 participants. The overall incidence of T2DM was 10.57/1000 person-years. Table 1 summarizes the characteristics of the study population at baseline. Compared with non-diabetic subjects at follow-up, T2DM patients were older and more frequently had a family history of T2DM; higher BMI, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), and PP; higher FPG, TC, TG and LDL-C levels; and lower HDL-C level at baseline ($P < 0.05$).

3.2. Association between high PP and incident T2DM (Table 2)

For females, the univariate Cox regression analysis revealed that the risk of T2DM was increased with high PP during follow-up [HR (95%CI) = 2.030 (1.638–2.516), $P < 0.0001$], but on the multivariate Cox regression analysis after adjustment for potential risk factors, the risk of T2DM was not associated with high PP [HR (95%CI) = 1.304 (0.979–1.736), $P = 0.0695$] or had a weak association [HR (95%CI) = 1.338 (1.003–1.783), $P = 0.0475$]. However, with PP from 70 to 76 mm Hg, risk of T2DM was associated with high PP in females after all adjustments for potential risk factors ($P < 0.05$). Furthermore, the impact of high PP on risk incident T2DM in females increased with adjustment on univariate Cox regression analysis (P-value for trend < 0.0001). However, risk of T2DM was not associated with high PP in males ($P > 0.05$).

3.3. Risk of T2DM stratified by quartiles of age (Table 3)

Both univariate and multivariate Cox regression analysis demonstrated that high PP was associated with risk of T2DM in females aged 52 to 59. The crude HR (95%CI) for incident T2DM was1.669 (1.166–2.387), as well as the adjusted HRs (95%CI) were 2.263

Table 1
Clinical and biochemical characteristics of the study cohort with and without type 2 diabetes mellitus (T2DM) at baseline (n = 12,272).

Variables	T2DM (n = 775)	Non-T2DM (n = 11,497)	χ^2/Z value	P value
Sex (male/female)	296/479	4368/7129	0.0125	0.9111
Age	53.00 (44.50–60.00)	50.00 (41.00–59.00)	5.7766	<0.0001[a]
Family history of T2DM[b]	67 (11.30)	586 (6.20)	20.0843	<0.0001
Current Smokers	197 (25.42)	3071 (26.71)	0.6203	0.4309
Alcohol intake	92 (11.87)	1283 (11.16)	0.3695	0.5433
Physical activity level				
Low	372 (48.00)	5736 (49.89)	2.5875	0.2742
Moderate	160 (20.65)	2467 (21.46)		
High	243 (31.35)	3294 (28.65)		
BMI (kg/m^2)	26.23 (23.73–28.67)	23.93 (21.64–26.37)	15.6153	<0.0001[a]
WC (cm)	88.95 (81.50–95.83)	81.35 (74.60–88.65)	17.3552	<0.0001[a]
SBP (mm Hg)	129.67 (118.17–142.67)	121.67 (111.00–135.67)	10.4864	<0.0001[a]
DBP (mm Hg)	81.67 (74.50–89.67)	77.33 (70.33–85.33)	9.9944	<0.0001[a]
FPG (mmol/L)	5.93 (5.41–6.40)	5.28 (4.96–5.63)	23.6891	<0.0001[a]
TC (mmol/L)	4.62 (4.08–5.21)	4.36 (3.81–4.99)	7.5786	<0.0001[a]
TG (mmol/L)	1.81 (1.23–2.62)	1.33 (0.95–1.90)	14.2341	<0.0001[a]
HDL-C (mmol/L)	1.09 (0.0.95–1.25)	1.15 (0.99–1.33)	−6.7973	<0.0001[a]
LDL-C (mmol/L)	2.60 (2.20–3.10)	2.50 (2.10–3.00)	3.6591	0.0003[a]
PP (mm Hg)	48.17 (40.17–56.50)	44.33 (38.00–52.67)	7.3982	<0.0001[a]

Data are median (interquartile range) or no. (%).
BMI body mass index, WC waist circumference, SBP systolic blood pressure, DBP diastolic blood pressure, FPG fasting plasma glucose, TC total cholesterol, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, PP pulse pressure.
[a] Mann–Whitney Wilcoxon test.
[b] Partial data deletion.

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