Is pulse pressure a predictor of diabetes in Chinese Han nationality population? 15-year prospective study in Chengdu community

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Diabetes mellitus (DM) has posed a significant economic burden to individuals, families and nations in recent years [1]. Prevention becomes a major public health priority in developing nations for its rapidly growing in incidence. Therefore, there is of great interest in identifying individuals at high risk of developing diabetes. Several studies have shown the importance of arterial blood pressure (BP) as a predictor of new-onset diabetes [2–4]. However, studies usually focused on systolic blood pressure (SBP), diastolic blood pressure (DBP) rather than pulse pressure, which is also a component of blood pressure. Pulse pressure (PP) has an important value in predicting cardiovascular events [5]. As a parameter of arterial elasticity, recent studies have reported an association among increased arterial stiffness, impaired glucose metabolism, metabolic syndrome and insulin resistance [6–8]. Some studies have reported that PP was an independent risk factor for new-onset diabetes mellitus in kidney transplantation or hypertensive patients [9–11]. These findings suggest a possible association between increased pulse pressure and new-onset diabetes, but little literature has examined the association in general population patients. Therefore, the aim of study was to determine whether pulse pressure would be associated with risk of new-onset diabetes based on the follow-up of data over 15 years collected from general Chinese community residents.

As one of the centers (Sichuan, China) in Chinese Multi-provincial Cohort Study (CMCS), a total of 687 individuals in an urban community located in Chengdu, Sichuan province, China were included for CVD risk factors survey according to the Multinational Monitoring of trends and determinants in Cardiovascular disease (MONICA) protocol [12]. Standardized questionnaire, physical examination and laboratory tests were included in this survey. The questionnaire included subjects' demographic characteristics, CVD risk factors containing smoking status, alcohol consumption levels, physical activity and family history of CVD. The physical examination included measurement of blood pressure, height, weight and so on. Fasting plasma glucose (FPG), fasting serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were included in laboratory tests. The same cohort also accepted a health examination in 2007 with the same methods. The detailed information of these participants has been reported elsewhere [13]. This study was approved by the Ministry of Health of China, as well as by the Ethics Committee of West China Hospital of Sichuan University. All participants provided written informed consent. Related definitions of hypertension, diabetes mellitus, smoking, alcohol intake and physical activity have been reported elsewhere [14,15].

Differences of baseline characteristics between participants with and without diabetes were tested by Student's *t* test for normally distributed variables and by the nonparametric Mann–Whitney or Wilcoxon test for skewed variables. Frequency analysis was performed with Chi-square test. Cox's proportional hazards regression models were used to estimate the hazard ratios (HRs), and the discriminatory power of anthropometric measures for diabetes was assessed by the area under the receiver operating curve (ROC). Fractional pulse pressure (PPf) and pulse pressure index (PPi) were also evaluated the predictive value of new-onset diabetes by multiple Cox regression analysis: the former is calculated as PP divided by mean arterial pressure (MAP), which is thought to be a better parameter reflecting arterial stiffness than PP which theoretically cancels out the influence of cardiac output and peripheral vascular resistance [11] and the latter is defined as PP divided by SBP, which was found as a new index assess incidence of cardiovascular and cerebrovascular diseases in Chinese population [16]. All BP measures were not included simultaneously in regression analysis to avoid co-linearity that these independent variables may have.

There were 687 eligible subjects studied at baseline completed the 7–8 years and the 15-year follow-up. The incidence of diabetes was 2.8% (n = 19) at 7–8 years and 10.8% (n = 74) at 15 years. About 67% (50/74) of the developed diabetes patients were self-reported history during the 15-year follow-up. Among the self-reported cohorts, 37 individuals were on antidiabetic drugs. The average FPG of the other 24 diagnosed DM individuals was 9.5 mmol/L. The median was 9.1 mmol/L and the maximum and minimum were 16.2 mmol/L and 7.1 mmol/L, respectively. Time of diabetes onset was 11.2 ± 3.8 years. Table 1 showed characteristics of participants at baseline. Compared with the subsequent nondiabetic subjects, the demographic data in 1992 showed that subsequent diabetic subjects had a higher BMI, fasting plasma glucose, and triglycerides at 7–8 years and 15-year follow-up (all $P < 0.001$, Table 1). The univariate Cox's proportional hazards regression analysis presented that PP and PP * HR could statistically increase the risk for the new onset of diabetes with a 15-year follow-up (Table 2). However, in the multivariate Cox's proportional hazards regression models, both PP and PP * HR were not significantly associated with risk of diabetes after adjustment for potential risk factors (Table 2). The areas under the ROC curves were 0.568 (95% CI: 0.530–0.606, $P = 0.368$) for PP at 7–8-year follow-up and 0.561 (95% CI: 0.523–0.599, P = 0.084) at 15-year follow-up (Table 3). Table 3 indicated that BMI were better than PP, PPf and PP * HR for predicting incident diabetes both at 7–8 years and 15-year follow-up in Chinese Han nationality population from Chengdu community.

The study demonstrated that PP, as an indirect indicator of arterial stiffness, could not be a predictor of diabetes in middle-aged population from community both at 7–8 years and 15 years follow-up. Different from our results, a subanalysis of Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial, Yasuno S et al. considered pulse pressure was an independent predictor of new-onset diabetes in high-risk Japanese hypertensive patients and increased arterial stiffness may be the cause in the development of diabetes [11]. However, we focused on the general community population not high-

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Table 1
Baseline characteristics of the population according to diabetes status at follow-up at 7–8 and 15 years.

Variable	Diabetes status at 7–8 years follow-up			Diabetes status at 15 years follow-up		
	Subsequent diabetic patients (n = 19)	Subsequent non-diabetic patients (n = 668)	*P* value	Subsequent diabetic patients (n = 74)	Subsequent non-diabetic patients (n = 613)	*P* value
Ages	50.6 ± 6.6	48.1 ± 6.2	0.082	49.8 ± 5.7	47.9 ± 6.2	0.013
Sex (male)	12 (63.1)	387 (57.9)	0.650	48 (64.9)	351 (57.3)	0.211
BMI (kg/m^2)	25.4 ± 3.6	23.3 ± 2.8	0.002	25.1 ± 3.3	23.2 ± 2.6	<0.001
SBP (mm Hg)	119.1 ± 18.7	114.4 ± 15.2	0.186	118.9 ± 18.2	114.0 ± 14.9	0.021
DBP (mm Hg)	75.8 ± 10.1	73.6 ± 9.1	0.298	75.7 ± 9.6	73.4 ± 9.0	0.095
PP (mm Hg)	43.3 ± 12.7	40.8 ± 9.5	0.404	43.2 ± 11.8	40.5 ± 9.3	0.022
MAP (mm Hg)	90.3 ± 12.2	87.2 ± 10.6	0.219	90.1 ± 11.8	87.0 ± 10.5	0.017
PPf	0.48 ± 0.11	0.47 ± 0.09	0.617	0.48 ± 0.10	0.47 ± 0.09	0.308
PPi	0.36 ± 0.07	0.35 ± 0.05	0.701	0.36 ± 0.06	0.35 ± 0.05	0.340
HR	83 ± 8	80 ± 9	0.197	82 ± 10	80 ± 9	0.090
PP * HR (P50, min–max)	3220 (1344–5280)	3124 (1768–8120)	0.119	3298 (1344–8120)	3108 (1768–6720)	0.019
FPG (mmol/L)	4.7 ± 0.8	4.3 ± 0.7	0.007	4.6 ± 0.8	4.2 ± 0.7	<0.001
TC (mmol/L)	4.6 ± 0.7	4.5 ± 0.8	0.377	4.7 ± 0.7	4.5 ± 0.8	0.023
TG (mmol/L)	2.97 ± 1.51	2.08 ± 0.96	<0.001	2.6 ± 1.2	2.1 ± 0.9	<0.001
LDL-C (mmol/L)	2.0 ± 1.0	2.3 ± 0.8	0.119	2.3 ± 0.9	2.3 ± 0.8	0.776
HDL-C (mmol/L)	1.29 ± 0.33	1.24 ± 0.23	0.413	1.18 ± 0.24	1.25 ± 0.24	0.007
Smoking	8 (42.1)	240 (35.9)	0.581	32 (43.2)	216 (35.2)	0.176
Alcohol intake	3 (15.8)	84 (12.6)	0.678	12 (16.2)	75 (12.2)	0.331
Physical activity	2 (10.5)	144 (21.6)	0.247	14 (18.9)	132 (21.5)	0.604
Hypertension	3 (15.8)	101 (15.1)	0.936	16 (21.6)	88 (14.4)	0.099
Family history of diabetes	4 (21.1)	22 (3.3)	<0.001	6 (8.1)	20 (3.3)	0.039

risk hypertensive patients. Our sub-analysis, excluding patients with hypertension at baseline, also confirmed the result: PP could not predict the occurrence of diabetes in general community population [n = 583, including 58 patients diagnosed DM, HR = 0.992 (95% CI: 0.957–1.027), *P* = 0.64]. Meanwhile, our study crowd was younger at baseline (48.13 ± 6.22 years). Epidemiological data indicate that PP increases significantly only after the fifth decade, suggesting that stiffening of the large arteries occurs predominantly in later life [17]. Therefore, PP is not suitable as an indicator for predicting risk of diabetes in middle-aged community residents.

In several studies about new-onset diabetes mellitus after kidney transplantation, pulse pressure was seemed as an independent risk factor which is believed to be the consequence of progressive stiffening of large arteries, and reflects diseased arterial walls [9,10]. PP has also a predictive value of cardiovascular events in patients with diabetes mellitus [18]. Increased arterial rigidity can be a component of the association between cardiovascular risk factors and the development of atherosclerosis. We suggested that PP could be a risk factor for the progression of these patients, however, these cross-sectional studies only showed the association with present risk factor conditions as well as did not allow for any firm conclusions regarding causality: a "Chicken-or-the-Egg" Question between PP and vascular stiffness. The Asklepios study demonstrates that large artery stiffening is only apparent in type-2 diabetes rather than in IFG, and greater operant PP in subjects with IFG is the result from their higher MAP [19]. Interestingly, in a diet-induced obese mice study, arterial stiffness develops within 1 month of the initiation of the diet and precedes the development of hypertension by 5 months [20]. Combined with our findings, PP, an indirect indicator of arterial stiffness, may reduce the predictive power of arterial stiffness predicting risk of diabetes in middle-aged community residents for inaccurately and untimely reflecting development in stiffening of large arteries.

For a higher stroke volume and prolonged diastolic period after a reduction in heat rate, PP can be influenced by heat rate directly. Therefore, HR may contribute to diminishing the increase in PP due to arterial stiffness and thus to underestimation of the predicted value of diabetes. PP * HR was calculated to integrate these two opposing factors [21]. Our result also shows no statistically significant with PP * HR in predicting diabetes. In fact, PP reflects a complex interaction of the heart and the vascular systems. Cardiac parameters (e.g. diastolic filling and contractility) can affect PP [22]. The dependence of PP on hemodynamic factors and vessel stiffness makes it an imperfect indicator of conduit vessel function and thus to be an inappropriate predictor in diabetes.

There were some limitations of our study. The first was that this study had relatively small sample size. This limited study could not analyze the association between PP with diabetes risk classified by gender. But we still can get some clues. The second was the way to diagnose diabetes mellitus. During the investigation, taken into account the financial and feasibility, we had not diagnose diabetes by oral glucose tolerance test, which means some individuals would

Table 2
Univariate and multivariate COX regression models for prediction of diabetes in different models.

Variable	Univariate regression		Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
PP (mm Hg)	1.025 (1.003–1.047)	0.024	1.009 (0.986–1.033)	0.429	1.003 (0.981–1.026)	0.771
PPf	3.747 (0.286–49.073)	0.314	1.327 (0.94–18.759)	0.834	0.864 (0.062–11.979)	0.913
PPi	8.828 (0.093–834.614)	0.348	1.482 (0.014–154.806)	0.868	0.747 (0.007–74.965)	0.901
HR * PP[a]	13.45 (1.75–103.35)	0.012	2.929 (0.344–24.956)	0.326	1.653 (0.197–13.862)	0.643

Model 1: adjusted for age, sex, smoking, alcohol intake, regular physical exercise, family history of diabetes, BMI.
Model 2: adjusted for age, sex, smoking, alcohol intake, regular physical exercise, family history of diabetes, BMI, HDL, TG and FPG.
[a] Transform to Log (HR * PP) to meet normal distribution.