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Nonlinear relationship between pulse pressure and the risk of prediabetes: a secondary retrospective Chinese cohort study

Running title: PP and Pre-DM risk

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Abstract

Objective: Previous research has shown that pulse pressure (PP) has a significant role in the start and development of type 2 diabetes mellitus. However, there is little proof that PP and prediabetes (Pre-DM) are related. Our study aimed to investigate the relationship between PP and incident Pre-DM in a substantial cohort of Chinese participants.

Design: The 'DATADRYAD' database (www.Datadryad.org) was used to retrieve the data for this secondary retrospective cohort analysis.

Participants: Data from 182672 Chinese individuals who participated in the medical examination program were recorded in this retrospective cohort study between 2010 and 2016 across 32 sites and 11 cities in China.

Setting: PP assessed at baseline and incident Pre-DM during follow-up were the target-independent and dependent variables. The association between PP and Pre-DM was investigated using Cox proportional hazards regression.

Primary outcome measures: The outcome was incident Pre-DM. Impaired fasting glucose levels (fasting blood glucose between 5.6 and 6.9 mmol/L) were used to define Pre-DM.

Results: After controlling for confounding variables, PP was positively correlated with incident Pre-DM among Chinese adults (HR: 1.009, 95%CI: 1.007-1.010). Additionally, at a PP inflection point of 29 mmHg, a nonlinear connection between the PP and incident Pre-DM was discovered. Increased PP was an independent risk factor for developing Pre-DM when PP was greater than 29 mmHg. However, their association was not significant when PP was less than 29 mmHg. According to subgroup analyses, females, never smokers, and non-obesity correlated more significantly with PP and Pre-DM.

Conclusion: We discovered that higher PP independently correlated with Pre-DM risk in this study of Chinese participants. The connection between PP and incident Pre-DM was also nonlinear. High PP levels were related to a higher chance of developing pre-DM when PP was above 29 mmHg.

Article Summary

Article focus

Our study investigated the relationship between PP and incident Pre-DM in a secondary retrospective cohort of Chinese participants.

Key Messages

We found that elevated PP was independently associated with an increased risk of Pre-DM in our study involving Chinese participants.

Higher PP levels were associated with a greater risk of developing Pre-DM when PP exceeded 29 mmHg.

Further investigation is needed to understand PP's impact on the incident Pre-DM.

Strengths and limitations of this study

Our research leveraged a substantial sample size, drawing participants from multiple centers, thus ensuring a robust representation of the Chinese population.

We elucidated a nonlinear relationship, marking the pioneering effort to pinpoint the inflection point of PP's impact on Pre-DM.

Our subgroup analysis allowed us to delve into other potential risk factors within the PP and incident Pre-DM association.

Our study did not incorporate a 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements, which could potentially lead to an underestimation of the incidence of Pre-DM.

Introduction

Prediabetes (Pre-DM) is intermediate hyperglycemia below the diagnostic cutoff for type 2 diabetes mellitus (T2DM). Patients with Pre-DM have been reported to have a higher risk for cardiovascular disease and nephropathy, indicating that impaired glucose begins to have a pathogenic effect at this early stage of diabetes[1]. The prevalence of Pre-DM is increasing globally with an aging population, urbanization, and changing lifestyles. From 2008 to 2017, the prevalence of Pre-DM in China has climbed from 15.5%[2] to 35.2%[3], creating a significant public health burden. Approximately 70% of subjects with Pre-DM will eventually get T2DM[4]. Numerous studies looked for ways to pinpoint the causes of diabetes and Pre-DM to prevent and cure the disease in its earliest stages.

Pulse pressure (PP) is referred to as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). Clinically, PP is the manifestation of atherosclerosis[5]. Compared to their non-diabetic contemporaries, people with T2DM have greater atherosclerosis, which results in a broad PP[5]. A greater risk of cardiovascular disease (CVD) exists in T2DM patients[6]. In addition, an increase in PP is another risk factor for CVD incidence and positively correlates with mortality[7-9]. Additionally, compared to healthy individuals, prediabetic patients have a greater burden from coronary atherosclerosis[10]. Notably, the atherosclerosis burden began to develop even before T2DM's clinical symptoms[10]. PP was found to be a significant risk factor for T2DM in a recent retrospective cohort investigation of a sizable sample[11]. However, whether prediabetes in Chinese adults is associated with PP is unknown. This study sought to analyze the precise correlation between PP and the likelihood of developing Pre-DM in Chinese participants.

Methods

Data source

Researchers can obtain original research data for free via the Dryad Digital Repository. The Dryad data repository's data on 211833 Chinese persons was downloaded[12]. The current research employed openly available data from a medical examination program as a secondary inquiry. Researchers may use the data for secondary analysis in accordance with the Dryad terms of service without interfering with the interests of the authors.

Study population

Each participant conducted under the Rich Healthcare Group Review Board, gave their written informed permission before taking part[12]. In addition, the Declaration of Helsinki was followed during our research. The necessary standards and legislation were followed in the execution of all procedures, including the declarations in the Declarations section.

Individuals were excluded from the investigation under these conditions: (1) diabetes at baseline; (2) diabetes or not defined diabetes status at follow-up; (3) abnormal body mass index (BMI) values (BMI over 55 or less than 15 kg/m²); (4) lacking data on baseline fasting plasma glucose (FPG), FPG at follow-up, height, DBP, gender, weight, and SBP; (5) FPG>6.9mmol/L during follow-up and FPG≥5.6mmol/L at baseline; (6) follow-up interval < 2 years; (7) PP outliers (three standard deviations above or below the mean). Finally, 182672 subjects eventually entered the study. The study's design and participant flow are shown in Figure 1.

Data collection

Trained staff members gathered and compiled all of the data. Data from laboratory inspections were gathered in the original study under uniform conditions using standardized handling

procedures. The skilled personnel, including height, blood pressure, body weight, and age, gathered demographic information. Professional trainees without light clothing and shoes measure individuals for weight and height. Weight/Height^2 (kg/m^2) was used to compute BMI. Trained staff members took blood pressure using a standard mercury sphygmomanometer. A Beckman 5800 autoanalyzer was used to measure laboratory data, such as low-density lipoprotein cholesterol (LDL-C), FPG, total cholesterol (TC), aspartate aminotransferase (AST), blood urea nitrogen (BUN), triglyceride (TG), alanine aminotransferase (ALT), serum creatinine (Scr), and high-density lipoprotein cholesterol (HDL-C). SBP (mmHg) - (DBP (mmHg)) were the formulas used to compute PP.

Diagnosis of Pre-DM

Impaired fasting glucose levels (FPG between 5.6 and 6.9 mmol/L) were used to define Pre-DM[13].

Statistical analysis

R software version 3.4.3 and EmpowerStats (R) version 4.0 were used for all statistical analyses.

We initially assessed the baseline data distribution by categorizing it into quartiles based on the PP (Q1$\leq$ 36; 36< Q2 $\leq$43; 43 < Q3 $\leq$50; 50< Q4). Continuous data were reported as medians with interquartile ranges (25th-75th percentile) or means with standard deviations (SD), while categorical data were expressed as frequencies and percentages. The Kruskal-Wallis H test, chi-square test, and one-way ANOVA were employed to assess disparities between PP groups. The cumulative incidence and terms person-year were used to represent incidence rates[14]. Comparisons of survival and cumulative event rates were done using the Kaplan-Meier method.

Using the log-rank test, we also examined the Kaplan-Meier hazard ratios (HR) of unfavorable events [15].

There were 133257 (72.32%), 4240 (2.30%), 1541 (0.84%),4209 (2.28%), 107684 (58.44%), 82879 (44.98%), 18563 (10.07%), 83382 (45.25%), 9759 (5.30%) and 133257 (72.32%) individuals with missing data for smoking status, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, and drinking status, respectively. The present study employed multiple imputations to handle the missing data of covariants. The imputation model included smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, FPG, sex, family history of diabetes, drinking status, and age. Processes for missing data analysis employ the assumption of missing at random[16].

This analysis assessed each factor's impact on incident Pre-DM using univariate Cox proportional hazards regression models. The multivariate Cox regression analysis also examined the precise connection between the PP and incident Pre-DM. In addition, we created three models (fully-adjusted, minimally-adjusted, and non-adjusted) to evaluate the connection between PP and incident Pre-DM. Suppose the HR is changed by at least 10% after the covariance is included in the model. At this point, the covariance should be adjusted[17].

The current analysis conducted several sensitivity analyses to determine if the findings were trustworthy. We converted PP into a categorical variable based on the quartile. We computed the P for the trend to verify the outcomes of the PP as the continuous variable and test for nonlinearity. Obesity and older adults were connected to a greater occurrence of Pre-DM. Thus, we excluded individuals with BMI $\geqslant 25 kg/m^2$ or age $\geqslant 60$ years for subsequent sensitivity analyses to examine the connection between PP and Pre-DM risk. Additionally, we incorporated the continuous covariate as a curve to the equation using a generalized additive model (GAM) to

confirm the validity of the results.

Considering PP is a continuous variable, we investigated potential nonlinear correlations between PP and Pre-DM using the Cox proportional hazards regression with cubic spline functions and smooth curve fitting. If the relationship proved nonlinear, a two-piecewise Cox proportional hazards regression model was applied to pinpoint the inflection point[18]. The study determined the most appropriate model for PP's connection with Pre-DM through log-likelihood ratio analysis.

Subgroup analysis, utilizing the Cox proportional hazard model, was also conducted. Subgroup variables included smoking status, age, BMI, family history of diabetes, gender, and drinking status. Stratification was performed based on medians or established clinical cut points[19], and variables such as age (<60, ≥60 years) and BMI (<25, ≥25 kg/m^2) were converted into categorical factors. Each stratum underwent a thoroughly adjusted analysis, except for the stratification factor. The likelihood ratio tests were conducted to ascertain subgroup interactions[20, 21]. The study adhered to the STROBE statement for all outcomes[17, 22]. Statistical significance was determined by a P-value < 0.05, using two-tailed tests.

Results

Characteristics of individuals

In the current research, 182672 individuals deemed free of Pre-DM at baseline were included. The average age was 40.832 ± 11.864 years, and 53.082% of individuals were male. Twenty thousand two hundred eighty-four individuals eventually got Pre-DM after an average of 3.143 years of follow-up. Table 1 displays comprehensive clinical measurements, biochemical tests, and various parameters. We categorized participants into subgroups based on PP quartiles (Q1≤ 36;

36< Q2 ≤43; 43< Q3≤50; 50< Q4). Compared to the Q1 group, the other groups (Q2 group, Q3 group, Q4 group) had higher ALT, BMI, age, TG, Scr, TC, AST, BUN, LDL-C, and lower HDL-C. Additionally, the Q4 group had a higher proportion of men, smokers, and drinkers.

The incidence rate of Pre-DM

During the follow-up, 20284 individuals developed incident Pre-DM, as outlined in Supplemental Table 1. All people had a prevalence rate of 11.10%. The four PP groups' prevalence rates were 8.92%, 9.47% (9.21%–9.73%), 10.82%, and 14.58%. In addition, the cumulative incidence rate of the overall population and four PP groups were 3532.68, 2779.24, 2999.95, 3470.06, and 4701.37 per 100,000 person-years, respectively. Individuals in the Q2, Q3, and Q4 groups exhibited significantly greater cumulative incidence and prevalence rates of Pre-DM than those in the Q1 group.

The Kaplan-Meier curves for the propensity to survive without Pre-DM are shown in Supplemental Figure 1. There was a significant difference between the four PP groups regarding the likelihood of developing Pre-DM (P 0.0001). As PP levels increased, the chance of living without prediabetes steadily dropped. As a result, Pre-DM risk was highest among those in the highest PP categories.

Univariate analysis

Supplemental Table 2 presents the findings of the univariate analysis. DBP, TC, BMI, SBP, FPG, age, TG, SCr, LDL-C, PP, and BUN were correlated with Pre-DM risk. HDL-C exhibits an inverse relationship with Pre-DM risk. Individuals who never drink or smoke also have a lower risk of developing pre-DM. Pre-DM risk was shown to be greater in men than in women.

The results of the connection between PP and Pre-DM

The Cox proportional hazard regression models for the association between PP and Pre-DM are shown in Table 2. In the non-adjusted model, the HR (95%CI) for the relationship between Pre-DM and PP was 1.025 (1.023-1.026). The HR (95%CI) in the minimally-adjusted model was 1.013 (1.011-1.014) after adjusting for smoking status, age, BMI, family history of diabetes, gender, and drinking status. The HR (95%CI) was 1.009 (1.007-1.010) in the fully-adjusted model after controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age. The findings showed that for every 1mmHg rise in PP, the risk of Pre-DM rose by 0.9%.

Sensitivity analyses

We used several sensitivity analyses to evaluate how reliable our results were. PP was changed from a continuous to a categorical variable before being reintroduced into the model. Following the translation of PP into categorical variables, the trend p was not equal, suggesting a potential nonlinear connection between PP and the chance of developing Pre-DM. Additionally, a GAM added the continuity covariate to the equation. Results for the GAM model showed a positive connection between PP and the probability of developing Pre-DM (HR: 1.008, 95%CI:1.007-1.010) (Table 2).

Besides, the current research excluded participants with BMI<25kg/m^2 for sensitivity analysis. After controlling for confounding factors, we observed a positive association between PP and Pre-DM risk (HR: 1.011, 95%CI: 1.009-1.013) (Supplemental Table 3). Moreover, we considered participants with ages < 60 years for sensitivity studies. After adjusting for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the results showed that PP remained positively correlated with the likelihood of

developing Pre-DM (HR: 1.008, 95%CI: 1.007-1.010). (Supplemental Table 3). According to the sensitivity analysis, our findings appeared to be solid.

The analysis of the nonlinear connection

The nonlinear connection between PP and incident Pre-DM is illustrated in Figure 2. After correcting for confounding factors, there was a nonlinear link between PP and incident Pre-DM (Table 3). Based on a two-piecewise Cox proportional hazards regression model, the PP's inflection point was 29 mmHg (P for log-likelihood ratio test = 0.008). When PP was more than 29 mmHg, PP was strongly linked with incident Pre-DM (HR:1.009, 95%CI: 1.008-1.011, P<0.0001). However, their correlation was not significant when PP was less than 29 mmHg (HR: 0.990, 95%CI: 0.977-1.003, P=0.1492).

The results of the subgroup analysis

In our investigation, subgroup analysis was used to examine other risk variables that could have altered the relationship between PP and incident prediabetes. We selected age, BMI, gender, family history of diabetes, smoking status, and drinking status as stratification variables and examined the changes in their impact sizes (Supplemental Table 4). Age, drinking status, and family history of diabetes had no impact on the correlation between PP and the risk of prediabetes. Females, never smokers, ever smokers, and subjects with BMI<25 kg/m^2 were more likely to be associated with prediabetes risk. Conversely, there was a weaker connection in males, current smokers, and individuals with BMI≥25 kg/m^2.

Discussion

The current study's main goal was to investigate the connection between PP and incident Pre-DM in Chinese participants. The findings demonstrated a correlation between increased PP

and a higher risk of prediabetes. The correlation between PP and Pre-DM was also investigated on the left and right sides of the inflection point. PP level and incident prediabetes have a nonlinear relationship. It was found that never-smokers, ever-smokers, females, and individuals with BMI<25 kg/m^2 had a greater correlation between PP and incident Pre-DM.

PP, the arithmetic difference between SBP and DBP, is determined by arterial wall elasticity and is related to all-cause mortality, cardiovascular events, stroke, kidney injury, severe eye illness, and arterial stiffness[23-28]. In comparison to blood pressure, PP has a better predictive capacity for poor cardiovascular outcomes in people with diabetes, according to several previous pieces of evidence[6, 29]. In addition, some studies found that PP demonstrated strong predictive ability in the homeostatic model assessment of insulin resistance index, diabetes, and metabolic syndrome[30-32]. In a retrospective study involving 211814 Chinese participants, after controlling for BMI, smoking and drinking status, age, TC, gender, family history of diabetes, FPG, TG, and BUN and ALT, Higher PP levels independently connect with increased T2DM risk (HR:1.003, 95%CI:1.001,1.005)[11]. In a longitudinal study involving 12272 Chinese, Zhang L et al.[30] found that high PP in Chinese women may be related to the development of T2DM after adjusting for confounding covariates. In a national cross-sectional study involving 6187 Korean older adults, Kwon YJ et al.[32] discovered a positive association between PP and metabolic syndrome after adjusting for alcohol consumption, smoking, age, regular exercise, and mean arterial blood pressure. In another cross-sectional cohort study that included 38708 rural Chinese participants, compared with the lowest group, the odds ratio (95%CI) of PP in the highest quartile of risk for metabolic syndrome was found to be 1.81 (1.67-1.95) after controlling for confounders[33]. In addition, in a prospective research enrolling 32917 Chinese, the HR (95%CI) for diabetes in the

Q3 and Q4 groups were 1.13 (1.04-1.22) and 1.14 (1.05-1.24), respectively, after adjusting for covariates compared to the Q1 group[34]. However, in a multicenter, longitudinal cohort study that included 18619 adults, high PP was not related to an increased risk of diabetes after adjusting for BMI, mean arterial pressure, gender, high-sensitivity C reactive protein, age, exercise, smoking, blood pressure lowering agents, drinking, hyperlipidemia, and family history of diabetes[35]. A retrospective study of 178 individuals with hypertension found that PP was not associated with the risk of new-onset diabetes after adjusting for potential confounders[36]. This retrospective cohort study involved 182672 Chinese individuals and revealed a higher incidence of prediabetes at increased PP levels. After adjusting for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the results indicated that each unit of the LAP raised the risk of prediabetes by 0.9%. Moreover, sensitivity analysis has demonstrated that this correlation remains observable in Chinese adults with age <60 years or BMI <25 kg/m^2. The efforts mentioned above have demonstrated the consistency of the connection between PP and Pre-DM risk. The findings offered a clinical PP-level intervention guideline to decrease Pre-DM risk.

Few previous studies have investigated the probable curvilinear link between PP and prediabetes. The current study first examined the nonlinear association between PP and prediabetes. After controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the findings revealed that the connection between PP and prediabetes was nonlinear. Based on a two-piecewise Cox proportional hazards regression model, we identified the inflection point of PP as 29 mmHg. When PP levels exceeded 29 mmHg, a 1-unit increase in PP correlated with a 0.9% increase in the

hazard ratio (HR) for individuals with Pre-DM (HR: 1.009, 95% CI: 1.008-1.011, P<0.0001). However, no significant correlation was observed between PP levels below 29 mmHg and the incident Pre-DM (HR: 0.990, 95% CI: 0.977-1.003, P = 0.1492). Elevated PP serves as a valuable indicator for identifying high-risk participants likely to develop Pre-DM during follow-up. This information can remind individuals to adopt healthier lifestyle habits sooner, ultimately improving their outcomes.

The mechanism behind the association between PP and prediabetes is yet unknown. Several explanations currently exist for PP leading to Pre-DM. Firstly, endothelial cell dysfunction may result in microvascular dysfunction[37], which in turn causes dysfunctional glucose metabolism, insulin resistance, poor tissue perfusion, and arterial stiffness[38-40]. Additionally, arterial stiffness may exacerbate microvascular lesions, creating a vicious cycle[41, 42]. Secondly, normal arteries can reduce PP, but arterial stiffness increases blood flow through low-resistance organs (such as the kidney and brain), which will cause organ dysfunction[43]. As a low-resistance, high-blood-flow organ with a mean tissue perfusion of 250–300 ml/min/100g, the pancreas may be negatively impacted by arterial stiffness in terms of its endocrine function.

The current research possesses several notable advantages. Firstly, we delved deeper into the nonlinear relationship between PP and prediabetes. Secondly, we minimized the impact of residual confounding factors through rigorous statistical adjustments. Thirdly, we conducted sensitivity analyses to ensure the robustness of our findings. Lastly, we performed a group analysis to evaluate other potential risk covariates that could affect the link between PP and Pre-DM.

The present study has certain limitations. First, because we used FPG levels to diagnose Pre-DM in this investigation, we might have overlooked some new cases of Pre-DM. Second, our

database lacks information on atherosclerosis, the use of antihypertensive medications, and the presence of hypertension. As a result, a sub-analysis based on the presence or absence of hypertension or the use of antihypertensive drugs was not possible. Third, SBP and DBP were only measured at baseline in the original study, and we did not assess how SBP and DBP changed over time. Future iterations of our investigation may incorporate additional confounding variables, such as variations in SBP and DBP during follow-up, hypertension, and antihypertensive medications. Consequently, we may consider utilizing a GAM model to explore the impact of changes in PP on future Pre-DM risk.

Conclusion

This cohort study of the Chinese population shows that PP was inversely and non-linearly associated with the incidence of Pre-DM after adjusting for other confounding factors. High PP levels were related to Pre-DM risk when PP was above 29 mmHg. From a therapeutic standpoint, lowering the PP below the inflection point represents a cost-effective and straightforward approach for the early prevention and intervention of Pre-DM.

Declarations

Ethics approval and consent to participate

The original study followed guidelines outlined by the Helsinki Declaration and was approved by the Rich Healthcare Group Review Board, as did our secondary retrospective cohort study. The information was retrieved retrospectively and patient consent was not required.

Consent for publication

Not applicable.

Availability of data and materials

The raw data can be downloaded from the 'DATADRYAD' database (www.Datadryad.org). Dryad Digital Repository. https://datadryad.org/stash/dataset/doi:10.5061/dryad.ft8750v.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Changchun Cao and Yong Han contributed to the study concept and design, researched and interpreted the data, and drafted the manuscript. Haofei Hu, Yongcheng He, and Jiao Luo analyzed the data and reviewed the manuscript. Changchun Cao and Yong Han oversaw the project's progress, contributed to the discussion, and reviewed the manuscript. Haofei Hu, Yongcheng He, and Jiao Luo were the guarantors of this work. As such, they had full access to all data in the study and were responsible for the data integrity and analysis accuracy. All authors read and approved the final manuscript.

Acknowledgments

Not applicable.

Table 1 The Baseline Characteristics of Participants

PP	Q1(≤36)	Q2(36 to ≤43)	Q3(43 to ≤50)	Q4(>50)	P-value
Participants	39914	47771	43811	51176	
Gender					<0.001
Male	16960 (42.491%)	22739 (47.600%)	24830 (56.675%)	32437 (63.383%)	
Female	22954 (57.509%)	25032 (52.400%)	18981 (43.325%)	18739 (36.617%)	
Age(years)	39.837 ± 9.945	39.905 ± 10.269	40.186 ± 11.236	43.028 ± 14.560	<0.001
Drinking status					
Current-drinker	526 (1.318%)	712 (1.490%)	682 (1.557%)	1004 (1.962%)	
Ex-drinker	3923 (9.829%)	5436 (11.379%)	5777 (13.186%)	7498 (14.651%)	
Never- drinker	35465 (88.854%)	41623 (87.130%)	37352 (85.257%)	42674 (83.387%)	
Smoking status					<0.001
Current-smoker	5468 (13.699%)	7191 (15.053%)	7324 (16.717%)	9441 (18.448%)	
Ex-smoker	1164 (2.916%)	1536 (3.215%)	1707 (3.896%)	2159 (4.219%)	
Never-smoker	33282 (83.384%)	39044 (81.732%)	34780 (79.386%)	39576 (77.333%)	
Family history of diabetes					<0.001
No	38974 (97.645%)	46764 (97.892%)	42922 (97.971%)	50379 (98.443%)	
Yes	940 (2.355%)	1007 (2.108%)	889 (2.029%)	797 (1.557%)	
SBP (mmHg)	104.383 ± 10.737	111.554 ± 10.604	119.000 ± 10.592	131.740 ± 12.760	<0.001
DBP (mmHg)	73.782 ± 10.685	72.461 ± 10.398	73.164 ± 10.347	74.508 ± 10.733	<0.001
BMI (kg/m2)	22.205 ± 3.119	22.654 ± 3.134	23.100 ± 3.184	23.773 ± 3.358	<0.001
AST(U/L)	21.2 (17, 26.6)	21.5 (17.2, 27)	22 (17.7, 27.8)	23(18.1, 28.7)	<0.001
ALT (U/L)	16 (11.6, 24)	16.6(12, 25.3)	18 (12, 27.4)	19.3(14, 29)	<0.001
HDL-C (mmol/L)	1.394 ± 0.312	1.384 ± 0.310	1.365 ± 0.304	1.351 ± 0.303	<0.001
TG (mmol/L)	0.94 (0.67, 1.40)	0.99 (0.70, 1.47)	1.04 (0.72, 1.55)	1.12 (0.79, 1.69)	<0.001
LDL-C (mmol/L)	2.651 ± 0.656	2.663 ± 0.660	2.685 ± 0.671	2.734 ± 0.690	
TC (mmol/L)	4.617 ± 0.858	4.632 ± 0.863	4.659 ± 0.880	4.725 ± 0.916	<0.001
BUN (mmol/L)	4.502 ± 1.142	4.538 ± 1.148	4.612 ± 1.156	4.732 ± 1.199	<0.001
SCr (umol/L)	67.116 ± 14.932	68.284 ± 15.134	70.240 ± 15.137	72.093 ± 16.223	
FPG (mmol/L)	4.691 ± 0.513	4.730 ± 0.497	4.772 ± 0.480	4.849 ± 0.450	<0.001
PP (mmHg)	30.601 ± 3.971	39.093 ± 1.979	45.836 ± 1.986	57.232 ± 6.395	

Values are n (%) or mean ± SD

PP: pulse pressure, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, ALT alanine aminotransferase, AST aspartate aminotransferase, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TC total cholesterol, TG triglycerides, Scr serum creatinine, BUN blood urea nitrogen, FPG fasting plasma glucose

Table 2 Relationship between PP and incident prediabetes in different models

Variable	Non-adjusted model (HR.,95% CI, P)	Minimally-adjusted model (HR,95% CI, P)	Fully-adjusted model (HR,95% CI, P)	GAM (HR,95% CI, P)
Total	1.025 (1.023, 1.026)	1.013 (1.011, 1.014)	1.009 (1.007, 1.010)	1.008 (1.007, 1.010)
PP	<0.00001	<0.00001	<0.00001	<0.00001
PP (quartile)				
Q1	ref	ref	ref	ref
Q2	1.125 (1.077, 1.176)	1.070 (1.024, 1.118)	1.043 (0.998, 1.090)	1.046 (1.001, 1.093)
	<0.00001	0.00263	0.06100	0.04505
Q3	1.347 (1.290, 1.407)	1.208 (1.156, 1.262)	1.131 (1.083, 1.181)	1.129 (1.080, 1.179)
	<0.00001	<0.00001	<0.00001	<0.00001
Q4	1.860 (1.787, 1.935)	1.408 (1.352, 1.467)	1.246 (1.197, 1.298)	1.238 (1.188, 1.291)
	<0.00001	<0.00001	<0.00001	<0.00001
P for trend	<0.00001	<0.00001	<0.00001	<0.00001

Crude model: we did not adjust for other covariants.

Minimally-adjusted model: we adjusted for gender, age, family history of diabetes, drinking status, smoking status, and BMI.

Fully-adjusted model: we adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

GAM: All covariates listed in Table 1 were adjusted. However, continuous covariates were adjusted as nonlinearity.

HR, hazard ratios; CI, confidence interval; Ref, reference; GAM, generalized additive mode; PP, pulse pressure.

Table 3 The result of the two-piecewise Cox proportional hazards regression model

Incident prediabetes	HR (95%CI)	P
Fitting model by standard linear regression	1.009 (1.007, 1.010)	<0.0001
Fitting model by two-piecewise Cox proportional hazards regression		
The inflection point of PP (mmHg)	29	
≤29	0.990 (0.977, 1.003)	0.1492
>29	1.009 (1.008, 1.011)	<0.0001
P for the log-likelihood ratio test	0.008	

We adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

HR, hazard ratios; CI, confidence; PP: pulse pressure

Figure 1 Study Population

Figure 2 The nonlinear relationship between PP and incident prediabetes. A nonlinear relationship between PP and incident prediabetes was detected after adjusting for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age.

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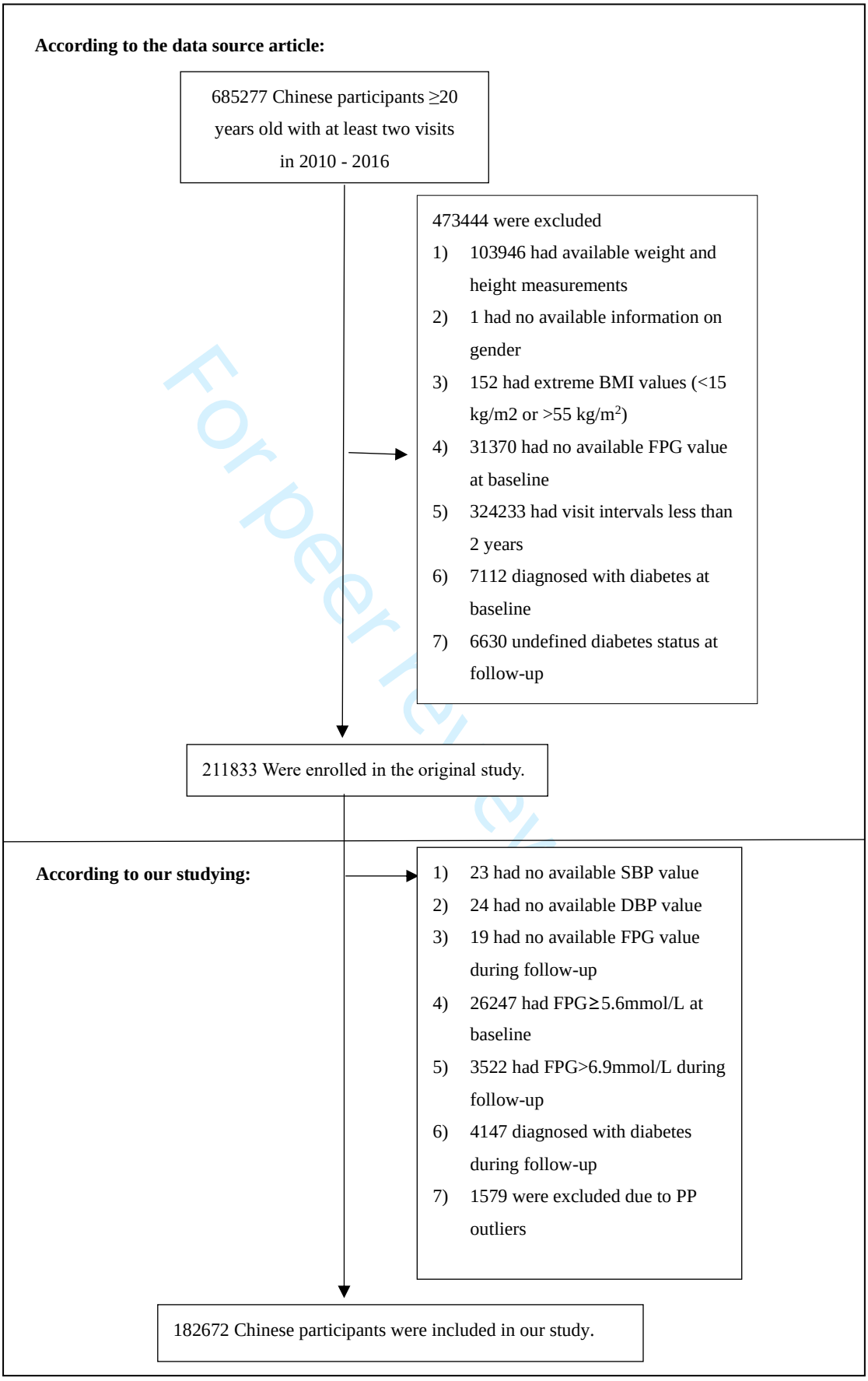
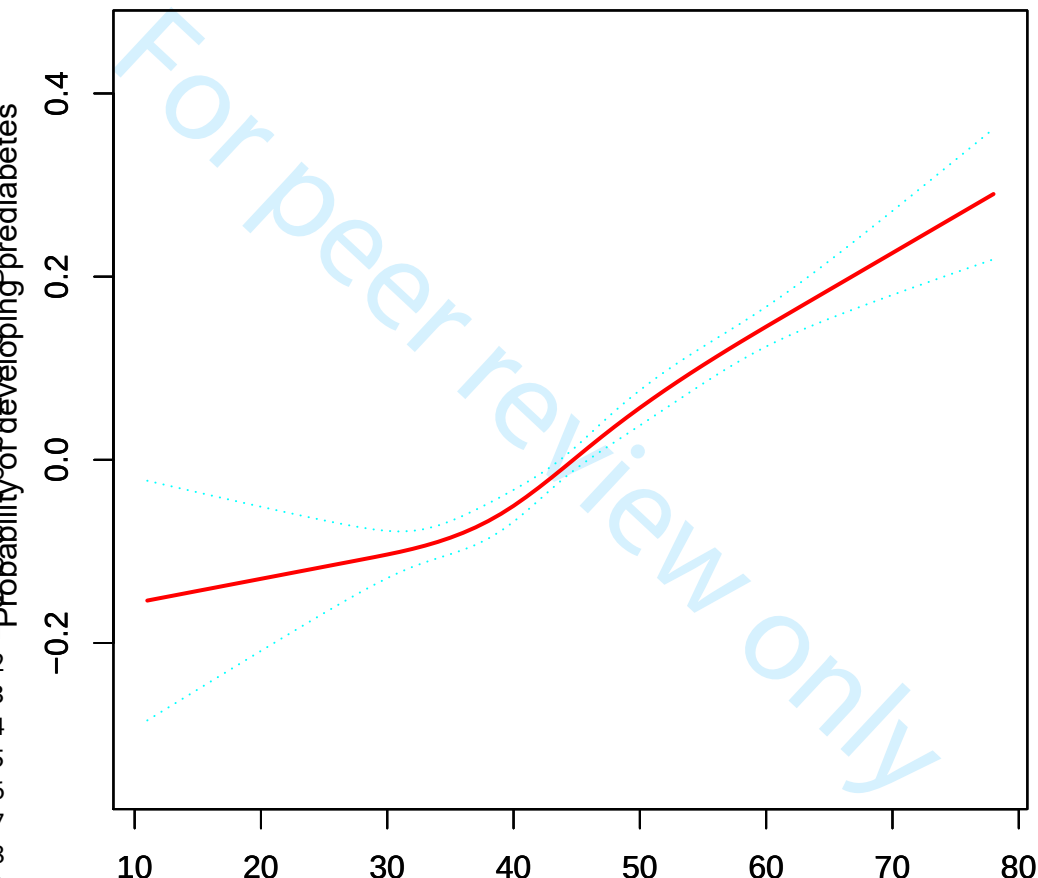




Supplemental Table 1 Incidence rate of incident prediabetes.

PP	Participants (n)	prediabetes events (n)	Cumulative incidence (95%CI) (%)	Per 100,000 person-year
Total	182672	20284	11.10 (10.96–11.25)	3532.68
Q1	39914	3560	8.92(8.64–9.20)	2779.24
Q2	47771	4525	9.47 (9.21–9.73)	2999.95
Q3	43811	4740	10.82 (10.53–11.11)	3470.06
Q4	51176	7459	14.58 (14.27–14.88)	4701.37
P for trend			<0.001	<0.001

PP: pulse pressure, CI: confidence interval

Supplemental Table 2 The results of the univariate analysis

	Statistics	HR (95%CI)	P value
Gender			<0.0001
Male	96966 (53.082%)	ref	
Female	85706 (46.918%)	0.627 (0.609, 0.645)	<0.00001
Age(years)	40.832 ± 11.864	1.033 (1.032, 1.034)	<0.00001
Drinking status			
Current-drinker	2924 (1.601%)	ref	
Ex-drinker	22634 (12.391%)	0.770 (0.701, 0.846)	<0.00001
Never- drinker	157114 (86.009%)	0.607 (0.556, 0.663)	<0.00001
Smoking status			
Current-smoker	29424 (16.108%)	ref	
Ex-smoker	6566 (3.594%)	0.896 (0.834, 0.963)	0.00286
Never-smoker	146682 (80.298%)	0.714 (0.691, 0.739)	<0.00001
Family history of diabetes			0.3503
No	179039 (98.011%)	ref	
Yes	3633 (1.989%)	1.054 (0.965, 1.153) 0.24372	
SBP (mmHg)	117.428 ± 15.208	1.026 (1.025, 1.027)	<0.00001
DBP (mmHg)	73.492 ± 10.572	1.029 (1.028, 1.030)	<0.00001
PP (mmHg)	43.936 ± 10.595	1.025 (1.023, 1.026)	<0.00001
BMI (kg/m2)	22.976 ± 3.259	1.124 (1.120, 1.129)	<0.00001
AST(U/L)	23.591 ± 12.164	1.005 (1.005, 1.006)	<0.00001
ALT (U/L)	23.232 ± 21.734	1.003 (1.003, 1.004)	<0.00001
HDL-C (mmol/L)	1.372 ± 0.307	0.739 (0.707, 0.773)	<0.00001
TG (mmol/L)	1.267 ± 0.934	1.200 (1.192, 1.208)	<0.00001
LDL-C (mmol/L)	2.685 ± 0.671	1.280 (1.256, 1.305)	<0.00001
TC (mmol/L)	4.661 ± 0.882	1.220 (1.202, 1.238)	<0.00001
BUN (mmol/L)	4.602 ± 1.167	1.136 (1.124, 1.149)	<0.00001
SCr (umol/L)	69.565 ± 15.522	1.006 (1.006, 1.007)	<0.00001
FPG (mmol/L)	4.765 ± 0.487	5.711 (5.513, 5.916)	<0.00001

PP: pulse pressure, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, ALT alanine aminotransferase, AST aspartate aminotransferase, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TC total cholesterol, TG triglycerides, Scr serum creatinine, BUN blood urea nitrogen, FPG fasting plasma glucose

Supplemental Table 3 Relationship between PP and prediabetes in different sensitivity analyses

Exposure	Model I (HR,95%CI, P)	Model II (HR,95%CI, P)
PP	1.011 (1.009, 1.013) <0.00001	1.008 (1.007, 1.010) <0.00001
PP (Quintile)		
Q1	Ref	Ref
Q2	1.055 (0.999, 1.115) 0.05494	1.040 (0.993, 1.090) 0.09739
Q3	1.166 (1.104, 1.232) <0.00001	1.123 (1.072, 1.177) <0.00001
Q4	1.310 (1.244, 1.379) <0.00001	1.228 (1.175, 1.285) <0.00001
P for trend	<0.00001	<0.00001

Model I was sensitivity analysis in participants without BMI≥25kg/m^2. We adjusted gender, age, family history of diabetes, drinking status, smoking status, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

Model II was sensitivity analysis in participants without age≥60 years. We adjusted gender, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

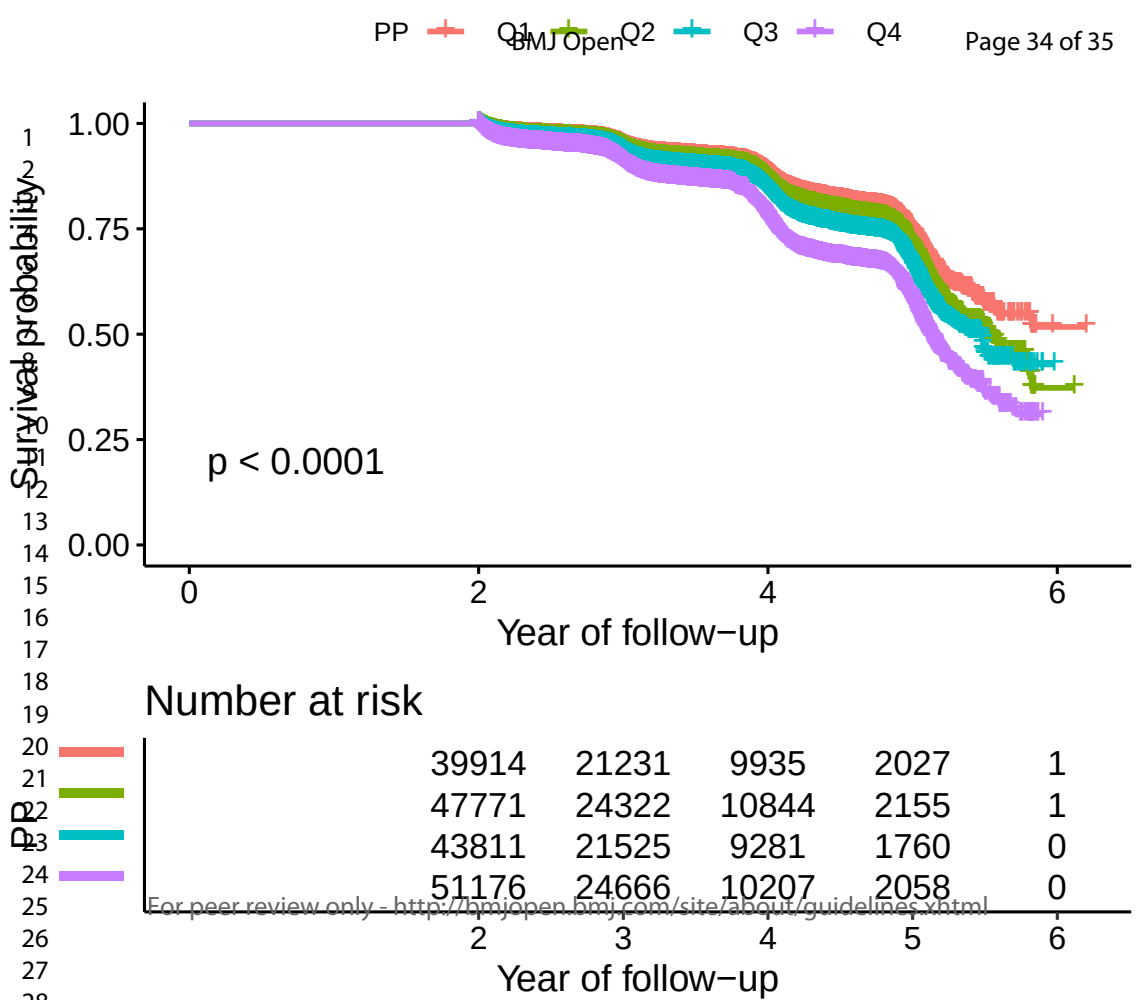
HR, hazard ratios; CI, confidence, Ref: reference; PP: pulse pressure

Supplemental Table 4 Effect size of PP on prediabetes in prespecified and exploratory subgroups

Characteristic	No of participants	HR (95%CI)	P value	P for interaction
Age, years				0.1335
<60	165813	1.008 (1.006, 1.009)	<0.0001	
≥60	16859	1.010 (1.007, 1.013)	<0.0001	
Gender				0.0002
Male	96966	1.006 (1.004, 1.008)	<0.0001	
Female	85706	1.011 (1.009, 1.013)	<0.0001	
BMI (kg/m^2)				<0.0001
<25	135554	1.012 (1.010, 1.014)	<0.0001	
≥25	47118	1.006 (1.004, 1.008)	<0.0001	
Smoking status				0.0075
Current smoker	29424	1.005 (1.002, 1.008)	0.0002	
Ever smoker	6566	1.007 (1.001, 1.013)	0.0211	
Never smoker	146682	1.010 (1.008, 1.011)	<0.0001	
Drinking status				0.2713
Current drinker	2924	1.014 (1.006, 1.022)	<0.0001	
Ever drinker	22634	1.007 (1.004, 1.010)	<0.0001	
Never drinker	157114	1.009 (1.007, 1.010)	<0.0001	
Family history of diabetes				0.0618
No	179039	1.009 (1.007, 1.010)	<0.0001	
Yes	3633	1.001 (0.992, 1.009)	0.9074	

Note 1: The above model was adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

Note 2: The model is not adjusted for the stratification variable in each case.



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Nonlinear relationship between pulse pressure and the risk of prediabetes: a secondary retrospective Chinese cohort study

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Blood Pressure, China, General diabetes < DIABETES & ENDOCRINOLOGY
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
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Nonlinear relationship between pulse pressure and the risk of prediabetes: a secondary retrospective Chinese cohort study

Running title: PP and Pre-DM risk

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Abstract

Objective: Previous research has shown that pulse pressure has a significant role in the start and development of type 2 diabetes mellitus. However, there is little proof that pulse pressure and prediabetes are related. Our study aimed to investigate the relationship between pulse pressure and incident prediabetes in a substantial cohort of Chinese participants.

Design: The 'DATADRYAD' database (www.Datadryad.org) was used to retrieve the data for this secondary retrospective cohort analysis.

Participants: Data from 182672 Chinese individuals who participated in the medical examination program were recorded in this retrospective cohort study between 2010 and 2016 across 32 sites and 11 cities in China.

Setting: Pulse pressure assessed at baseline and incident prediabetes during follow-up were the target-independent and dependent variables. The association between pulse pressure and prediabetes was investigated using Cox proportional hazards regression.

Primary outcome measures: The outcome was incident prediabetes. Impaired fasting glucose levels (fasting blood glucose between 5.6 and 6.9 mmol/L) were used to define prediabetes.

Results: After controlling for confounding variables, pulse pressure was positively correlated with incident prediabetes among Chinese adults (HR: 1.009, 95%CI: 1.007-1.010). Additionally, at a pulse pressure inflection point of 29 mmHg, a nonlinear connection between the pulse pressure and incident prediabetes was discovered. Increased pulse pressure was an independent risk factor for developing prediabetes when pulse pressure was greater than 29 mmHg. However, their association was not significant when pulse pressure was less than 29 mmHg. According to subgroup analyses, females, never smokers, and non-obesity correlated more significantly with

pulse pressure and prediabetes.

Conclusion: We discovered that higher pulse pressure independently correlated with prediabetes risk in this study of Chinese participants. The connection between pulse pressure and incident prediabetes was also nonlinear. High pulse pressure levels were related to a higher risk of prediabetes when pulse pressure was above 29 mmHg.

Article Summary

Article focus

Our study investigated the relationship between PP and incident Pre-DM in a secondary retrospective cohort of Chinese participants.

Key Messages

We found that elevated PP was independently associated with an increased risk of Pre-DM in our study involving Chinese participants.

Higher PP levels were associated with a greater risk of developing Pre-DM when PP exceeded 29 mmHg.

Further investigation is needed to understand PP's impact on the incident Pre-DM.

Strengths and limitations of this study

Our research leveraged a substantial sample size, drawing participants from multiple centers, thus ensuring a robust representation of the Chinese population.

We elucidated a nonlinear relationship, marking the pioneering effort to pinpoint the inflection point of PP's impact on Pre-DM.

Our subgroup analysis allowed us to delve into other potential risk factors within the PP and incident Pre-DM association.

Our study did not incorporate a 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements, which could potentially lead to an underestimation of the incidence of Pre-DM.

Introduction

Prediabetes (Pre-DM) is intermediate hyperglycemia below the diagnostic cutoff for type 2 diabetes mellitus (T2DM). Patients with Pre-DM have been reported to have a higher risk for cardiovascular disease and nephropathy, indicating that impaired glucose begins to have a pathogenic effect at this early stage of diabetes[1]. The prevalence of Pre-DM is increasing globally with an aging population, urbanization, and changing lifestyles. From 2008 to 2017, the prevalence of Pre-DM in China has climbed from 15.5%[2] to 35.2%[3], creating a significant public health burden. Approximately 70% of subjects with Pre-DM will eventually get T2DM[4]. Numerous studies looked for ways to pinpoint the causes of diabetes and Pre-DM to prevent and cure the disease in its earliest stages.

Pulse pressure (PP) is referred to as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). Clinically, PP is the manifestation of atherosclerosis[5]. Compared to their non-diabetic contemporaries, people with T2DM have greater atherosclerosis, which results in a broad PP[5]. A greater risk of cardiovascular disease (CVD) exists in T2DM patients[6]. In addition, an increase in PP is another risk factor for CVD incidence and positively correlates with mortality[7-9]. Additionally, compared to healthy individuals, prediabetic patients have a greater burden from coronary atherosclerosis[10]. Notably, the atherosclerosis burden began to develop even before T2DM's clinical symptoms[10]. PP was found to be a significant risk factor for T2DM in a recent retrospective cohort investigation of a sizable sample[11]. However, whether prediabetes in Chinese adults is associated with PP is unknown. This study sought to analyze the precise correlation between PP and the likelihood of developing Pre-DM in Chinese participants.

Methods

Data source

Researchers can obtain original research data for free via the Dryad Digital Repository. The Dryad data repository's data on 211833 Chinese persons was downloaded[12]. The current research employed openly available data from a medical examination program as a secondary inquiry. Researchers may use the data for secondary analysis in accordance with the Dryad terms of service without interfering with the interests of the authors.

Study population

The original study was approved by the Rich Healthcare Group Review Board. Hence, ethical approval was not required for this secondary analysis. Each participant conducted under the Rich Healthcare Group Review Board, gave their written informed permission before taking part[12]. In addition, the Declaration of Helsinki was followed during our research. The necessary standards and legislation were followed in the execution of all procedures, including the declarations in the Declarations section.

Individuals were excluded from the investigation under these conditions: (1) diabetes at baseline; (2) diabetes or not defined diabetes status at follow-up; (3) abnormal body mass index (BMI) values (BMI over 55 or less than 15 kg/m²); (4) lacking data on baseline fasting plasma glucose (FPG), FPG at follow-up, height, DBP, gender, weight, and SBP; (5) FPG>6.9mmol/L during follow-up and FPG≥5.6mmol/L at baseline; (6) follow-up interval < 2 years; (7) PP outliers (three standard deviations above or below the mean). Finally, 182672 subjects eventually entered the study. The study's design and participant flow are shown in Figure 1.

Data collection

Trained staff members gathered and compiled all of the data. Data from laboratory inspections were gathered in the original study under uniform conditions using standardized handling procedures. The skilled personnel, including height, blood pressure, body weight, and age, gathered demographic information. Professional trainees without light clothing and shoes measure individuals for weight and height. Weight/Height^2 (kg/m^2) was used to compute BMI. Trained staff members took blood pressure using a standard mercury sphygmomanometer. A Beckman 5800 autoanalyzer was used to measure laboratory data, such as low-density lipoprotein cholesterol (LDL-C), FPG, total cholesterol (TC), aspartate aminotransferase (AST), blood urea nitrogen (BUN), triglyceride (TG), alanine aminotransferase (ALT), serum creatinine (Scr), and high-density lipoprotein cholesterol (HDL-C). SBP (mmHg) - (DBP (mmHg)) were the formulas used to compute PP.

Diagnosis of Pre-DM

Impaired fasting glucose levels (FPG between 5.6 and 6.9 mmol/L) were used to define Pre-DM[13].

Patient and Public Involvement

Given this was a secondary retrospective cohort study, no patient was involved in the study.

Statistical analysis

R software version 3.4.3 and EmpowerStats (R) version 4.0 were used for all statistical analyses.

We initially assessed the baseline data distribution by categorizing it into quartiles based on the PP (Q1$\leq$ 36; 36< Q2 $\leq$43; 43 < Q3 $\leq$50; 50< Q4). Continuous data were reported as medians with interquartile ranges (25th-75th percentile) or means with standard deviations (SD), while

categorical data were expressed as frequencies and percentages. The Kruskal-Wallis H test, chi-square test, and one-way ANOVA were employed to assess disparities between PP groups. The cumulative incidence and terms person-year were used to represent incidence rates[14]. Comparisons of survival and cumulative event rates were done using the Kaplan-Meier method. Using the log-rank test, we also examined the Kaplan-Meier hazard ratios (HR) of unfavorable events [15].

There were 133257 (72.32%), 4240 (2.30%), 1541 (0.84%), 4209 (2.28%), 107684 (58.44%), 82879 (44.98%), 18563 (10.07%), 83382 (45.25%), 9759 (5.30%) and 133257 (72.32%) individuals with missing data for smoking status, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, and drinking status, respectively. The present study employed multiple imputations to handle the missing data of covariants. The imputation model included smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, FPG, sex, family history of diabetes, drinking status, and age. Processes for missing data analysis employ the assumption of missing at random[16].

This analysis assessed each factor's impact on incident Pre-DM using univariate Cox proportional hazards regression models. The multivariate Cox regression analysis also examined the precise connection between the PP and incident Pre-DM. In addition, we created three models (fully-adjusted, minimally-adjusted, and non-adjusted) to evaluate the connection between PP and incident Pre-DM. Suppose the HR is changed by at least 10% after the covariance is included in the model. At this point, the covariance should be adjusted[17].

The current analysis conducted several sensitivity analyses to determine if the findings were trustworthy. We converted PP into a categorical variable based on the quartile. We computed the P for the trend to verify the outcomes of the PP as the continuous variable and test for

nonlinearity. Obesity and older adults were connected to a greater occurrence of Pre-DM. Thus, we excluded individuals with BMI $\geqslant 25 kg/m^2$ or age $\geqslant 60$ years for subsequent sensitivity analyses to examine the connection between PP and Pre-DM risk. Additionally, we incorporated the continuous covariate as a curve to the equation using a generalized additive model (GAM) to confirm the validity of the results. We also calculated E-values to examine the possibility of unmeasured confounding between PP and the risk of prediabetes

We used Cox proportional hazards regression with cubic spline functions and smooth curve fitting to explore the nonlinear relationship between PP and Pre-DM. We first utilized a recursive technique to locate the inflection point if a non-linear relationship was discovered[18]. The recursive algorithm commences with an arbitrary initialization and subsequently undergoes a series of filtering and smoothing steps in order to identify the inflection point accurately. Following this, we construct a two-piece Cox proportional hazards regression model, separately analyzing the data on either side of the inflection point. Ultimately, the study determined the most appropriate model for PP's connection with Pre-DM through log-likelihood ratio analysis.

Subgroup analysis, utilizing the Cox proportional hazard model, was also conducted. Firstly, these variables were selected based on a combination of clinical relevance, literature review, and the availability of data within our cohort. Secondly, the interaction test between these variables and PP was performed before the subgroup analysis. The likelihood ratio test was used to compare models with and without the multiplicative interaction term. Secondly, stratification was performed based on medians or established clinical cut points[19], and variables such as age (<60, ≥60 years) and BMI (<25, ≥25 kg/m^2) were converted into categorical factors. Thirdly, a fully adjusted analysis was performed for each stratum, except for the stratification factor. Ultimately,

the likelihood ratio test was used to determine whether interaction terms existed in models with and without interaction terms[20, 21]. The study adhered to the STROBE statement for all outcomes[17, 22]. Statistical significance was determined by a P-value < 0.05, using two-tailed tests.

Results

Characteristics of individuals

In the current research, 182672 individuals deemed free of Pre-DM at baseline were included. The average age was 40.832 ± 11.864 years, and 53.082% of individuals were male. Twenty thousand two hundred eighty-four individuals eventually got Pre-DM after an average of 3.143 years of follow-up. Table 1 displays comprehensive clinical measurements, biochemical tests, and various parameters. We categorized participants into subgroups based on PP quartiles (Q1≤ 36; 36< Q2 ≤43; 43< Q3≤50; 50< Q4). Compared to the Q1 group, the other groups (Q2 group, Q3 group, Q4 group) had higher ALT, BMI, age, TG, Scr, TC, AST, BUN, LDL-C, and lower HDL-C. Additionally, the Q4 group had a higher proportion of men, smokers, and drinkers.

The incidence rate of Pre-DM

During the follow-up, 20284 individuals developed incident Pre-DM, as outlined in Supplemental Table 1. All people had a prevalence rate of 11.10%. The four PP groups' prevalence rates were 8.92%, 9.47% (9.21%–9.73%), 10.82%, and 14.58%. In addition, the cumulative incidence rate of the overall population and four PP groups were 3532.68, 2779.24, 2999.95, 3470.06, and 4701.37 per 100,000 person-years, respectively. Individuals in the Q2, Q3, and Q4 groups exhibited significantly greater cumulative incidence and prevalence rates of Pre-DM than those in the Q1 group.

The Kaplan-Meier curves for the propensity to survive without Pre-DM are shown in Supplemental Figure 1. There was a significant difference between the four PP groups regarding the likelihood of developing Pre-DM (P<0.0001). As PP levels increased, the chance of living without prediabetes steadily dropped. As a result, Pre-DM risk was highest among those in the highest PP categories.

Univariate analysis

Supplemental Table 2 presents the findings of the univariate analysis. DBP, TC, BMI, SBP, FPG, age, TG, SCr, LDL-C, PP, and BUN were correlated with Pre-DM risk. HDL-C exhibits an inverse relationship with Pre-DM risk. Individuals who never drink or smoke also have a lower risk of developing pre-DM. Pre-DM risk was shown to be greater in men than in women.

The results of the connection between PP and Pre-DM

The Cox proportional hazard regression models for the association between PP and Pre-DM are shown in Table 2. In the non-adjusted model, the HR (95%CI) for the relationship between Pre-DM and PP was 1.025 (1.023-1.026). The HR (95%CI) in the minimally-adjusted model was 1.013 (1.011-1.014) after adjusting for smoking status, age, BMI, family history of diabetes, gender, and drinking status. The HR (95%CI) was 1.009 (1.007-1.010) in the fully-adjusted model after controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age. The findings showed that for every 1mmHg rise in PP, the risk of Pre-DM rose by 0.9%.

Sensitivity analyses

We used several sensitivity analyses to evaluate how reliable our results were. PP was changed from a continuous to a categorical variable before being reintroduced into the model. Following

the translation of PP into categorical variables, the trend p was not equal, suggesting a potential nonlinear connection between PP and the chance of developing Pre-DM. Additionally, a GAM added the continuity covariate to the equation. Results for the GAM model showed a positive connection between PP and the probability of developing Pre-DM (HR: 1.008, 95%CI:1.007-1.010) (Table 2).

Besides, the current research excluded participants with BMI<25kg/m^2 for sensitivity analysis. After controlling for confounding factors, we observed a positive association between PP and Pre-DM risk (HR: 1.011, 95%CI: 1.009-1.013) (Supplemental Table 3). Moreover, we considered participants with ages < 60 years for sensitivity studies. After adjusting for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the results showed that PP remained positively correlated with the likelihood of developing Pre-DM (HR: 1.008, 95%CI: 1.007-1.010). (Supplemental Table 3). According to the sensitivity analysis, our findings appeared to be solid.

Additionally, an E-value was computed to assess the vulnerability of the study results to potential unobserved confounding factors. The resulting E-value (1.21) demonstrated a higher level of statistical significance in comparison to the relative risk (1.05) associated with unmeasured confounders and PP. This suggests that the impact of unmeasured or unidentified confounders on the relationship between PP and the occurrence of Pre-DM was negligible.

The analysis of the nonlinear connection

The nonlinear connection between PP and incident Pre-DM is illustrated in Figure 2. After correcting for confounding factors, there was a nonlinear link between PP and incident Pre-DM (Table 3). Based on a two-piecewise Cox proportional hazards regression model, the PP's

inflection point was 29 mmHg (P for log-likelihood ratio test = 0.008). When PP was more than 29 mmHg, PP was strongly linked with incident Pre-DM (HR:1.009, 95%CI: 1.008-1.011, P<0.0001). However, their correlation was not significant when PP was less than 29 mmHg (HR: 0.990, 95%CI: 0.977-1.003, P=0.1492).

The results of the subgroup analysis

Interaction tests performed before subgroup analyses showed that age, BMI, gender, family history of diabetes, smoking status, and drinking status interacted with PP (P<0.001) (Supplemental Table 4). We selected age, BMI, gender, family history of diabetes, smoking status, and drinking status as stratification variables and examined the changes in their impact sizes (Supplemental Table 5). Age, drinking status, and family history of diabetes had no impact on the correlation between PP and the risk of prediabetes. Females, never smokers, ever smokers, and subjects with BMI<25 kg/m^2 were more likely to be associated with prediabetes risk. Conversely, there was a weaker connection in males, current smokers, and individuals with BMI≥25 kg/m^2.

Discussion

The current study's main goal was to investigate the connection between PP and incident Pre-DM in Chinese participants. The findings demonstrated a correlation between increased PP and a higher risk of prediabetes. The correlation between PP and Pre-DM was also investigated on the left and right sides of the inflection point. PP level and incident prediabetes have a nonlinear relationship. It was found that never-smokers, ever-smokers, females, and individuals with BMI<25 kg/m^2 had a greater correlation between PP and incident Pre-DM.

PP, the arithmetic difference between SBP and DBP, is determined by arterial wall elasticity and is related to all-cause mortality, cardiovascular events, stroke, kidney injury, severe eye

illness, and arterial stiffness[23-28]. In comparison to blood pressure, PP has a better predictive capacity for poor cardiovascular outcomes in people with diabetes, according to several previous pieces of evidence[6, 29]. In addition, some studies found that PP demonstrated strong predictive ability in the homeostatic model assessment of insulin resistance index, diabetes, and metabolic syndrome[30-32]. In a retrospective study involving 211814 Chinese participants, after controlling for BMI, smoking and drinking status, age, TC, gender, family history of diabetes, FPG, TG, and BUN and ALT, Higher PP levels independently connect with increased T2DM risk (HR:1.003, 95%CI:1.001,1.005)[11]. In a longitudinal study involving 12272 Chinese, Zhang L et al.[30] found that high PP in Chinese women may be related to the development of T2DM after adjusting for confounding covariates. In a national cross-sectional study involving 6187 Korean older adults, Kwon YJ et al.[32] discovered a positive association between PP and metabolic syndrome after adjusting for alcohol consumption, smoking, age, regular exercise, and mean arterial blood pressure. In another cross-sectional cohort study that included 38708 rural Chinese participants, compared with the lowest group, the odds ratio (95%CI) of PP in the highest quartile of risk for metabolic syndrome was found to be 1.81 (1.67-1.95) after controlling for confounders[33]. In addition, in a prospective research enrolling 32917 Chinese, the HR (95%CI) for diabetes in the Q3 and Q4 groups were 1.13 (1.04-1.22) and 1.14 (1.05-1.24), respectively, after adjusting for covariates compared to the Q1 group[34]. However, in a multicenter, longitudinal cohort study that included 18619 adults, high PP was not related to an increased risk of diabetes after adjusting for BMI, mean arterial pressure, gender, high-sensitivity C reactive protein, age, exercise, smoking, blood pressure lowering agents, drinking, hyperlipidemia, and family history of diabetes[35]. A retrospective study of 178 individuals with hypertension found that PP was not

associated with the risk of new-onset diabetes after adjusting for potential confounders[36]. This retrospective cohort study involved 182672 Chinese individuals and revealed a higher incidence of prediabetes at increased PP levels. After adjusting for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the results indicated that each unit of the LAP raised the risk of prediabetes by 0.9%. Moreover, sensitivity analysis has demonstrated that this correlation remains observable in Chinese adults with age <60 years or BMI <25 kg/m^2. The efforts mentioned above have demonstrated the consistency of the connection between PP and Pre-DM risk. The findings offered a clinical PP-level intervention guideline to decrease Pre-DM risk.

Few previous studies have investigated the probable curvilinear link between PP and prediabetes. The current study first examined the nonlinear association between PP and prediabetes. After controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the findings revealed that the connection between PP and prediabetes was nonlinear. Based on a two-piecewise Cox proportional hazards regression model, we identified the inflection point of PP as 29 mmHg. When PP levels exceeded 29 mmHg, a 1-unit increase in PP correlated with a 0.9% increase in the hazard ratio (HR) for individuals with Pre-DM (HR: 1.009, 95% CI: 1.008-1.011, P<0.0001). However, no significant correlation was observed between PP levels below 29 mmHg and the incident Pre-DM (HR: 0.990, 95% CI: 0.977-1.003, P = 0.1492). Elevated PP serves as a valuable indicator for identifying high-risk participants likely to develop Pre-DM during follow-up. Moreover, our analysis revealed that the relationship between PP and the emergence of Pre-DM was more pronounced in never-smokers, ever-smokers, females, and individuals with BMI< 25

kg/m^2. In contrast, this association appeared attenuated in males, current smokers, and individuals with BMI ≥ 25 kg/m^2. Prior research has consistently identified obesity, smoking, and male as contributors to insulin resistance[37, 38], which is a precursor to Pre-DM. We postulated that the attenuated association observed in these subgroups may be attributable to the overriding influence of these risk factors on the pathogenesis of Pre-DM. The direct impact of PP on prediabetes risk may be somewhat eclipsed by the more substantial effects of obesity, active smoking, and the male sex on insulin resistance and subsequent Pre-DM development. This information can remind individuals to adopt healthier lifestyle habits sooner, ultimately improving their outcomes.

The mechanism behind the association between PP and prediabetes is yet unknown. Several explanations currently exist for PP leading to Pre-DM. Firstly, endothelial cell dysfunction may result in microvascular dysfunction[39], which in turn causes dysfunctional glucose metabolism, insulin resistance, poor tissue perfusion, and arterial stiffness[40-42]. Additionally, arterial stiffness may exacerbate microvascular lesions, creating a vicious cycle[43, 44]. Secondly, normal arteries can reduce PP, but arterial stiffness increases blood flow through low-resistance organs (such as the kidney and brain), which will cause organ dysfunction[45]. As a low-resistance, high-blood-flow organ with a mean tissue perfusion of 250–300 ml/min/100g, the pancreas may be negatively impacted by arterial stiffness in terms of its endocrine function.

The current research possesses several notable advantages. Firstly, we delved deeper into the nonlinear relationship between PP and prediabetes. Secondly, we minimized the impact of residual confounding factors through rigorous statistical adjustments. Thirdly, we conducted sensitivity analyses to ensure the robustness of our findings. Lastly, we performed a group analysis to evaluate other potential risk covariates that could affect the link between PP and Pre-DM.

The present study has certain limitations. First, this study is based on a Chinese population, and while it offers valuable insights, the findings might not be directly generalizable to other populations due to genetic, lifestyle, and environmental differences. In the future, we will explore the relationship between PP and prediabetes risk in diverse populations. Second, as our study was a secondary analysis, we cannot guarantee data quality monitoring and variable control. In forthcoming research endeavors, we will endeavor to construct prospective cohort studies with enhanced data quality oversight and variable control, thereby mitigating bias. Third, the original study excluded people with diabetes at baseline or those with missing data, which may have affected the representativeness of the sample. In the future, we will design our own study in a more diverse population to validate our findings. Fourth, prediabetes was defined based on impaired fasting glucose levels in our study. This could potentially lead to underestimation of prediabetes incidence. This is a secondary retrospective study, and the raw data did not provide information regarding 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements. In the future, we will consider designing our study to document more variables, including 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements. Fifth, as with all observational studies, there may be uncontrolled or unmeasured confounding factors, such as diet, exercise, atherosclerosis, the use of antihypertensive medications, and the presence of hypertension, despite controlling for known potential confounders like BMI, TC, LDL-C, AST, ALT, Scr, BUN, and FPG. However, we used the E-value to evaluate the impact of unmeasured confounders and determined it unlikely that they fully explained the results. Sixth, SBP and DBP were only measured at baseline in the original study, and we did not assess how SBP and DBP changed over time. In the future, we will consider designing our own study and

documenting more information, such as diet, exercise, atherosclerosis, antihypertensive medications, the presence of hypertension and changes in blood pressure over time, and then utilizing a GAM model to explore the impact of changes in PP on Pre-DM risk.

Conclusion

This cohort study of the Chinese population shows that PP was inversely and non-linearly associated with the incidence of Pre-DM after adjusting for other confounding factors. High PP levels were related to Pre-DM risk when PP was above 29 mmHg. From a therapeutic standpoint, lowering the PP below the inflection point represents a cost-effective and straightforward approach for the early prevention and intervention of Pre-DM.

Declarations

Ethics approval and consent to participate

The original study followed guidelines outlined by the Helsinki Declaration and was approved by the Rich Healthcare Group Review Board. In addition, the Rich Healthcare Group Review Board has waived informed consent for the current retrospective study. All methods were performed in accordance with the relevant the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article [and/or its supplementary materials].

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Changchun Cao and Yong Han contributed to the study concept and design, researched and interpreted the data, and drafted the manuscript. Haofei Hu, Yongcheng He, and Jiao Luo analyzed the data and reviewed the manuscript. Changchun Cao and Yong Han oversaw the project's progress, contributed to the discussion, and reviewed the manuscript. Haofei Hu, Yongcheng He, and Jiao Luo were the guarantors of this work. As such, they had full access to all data in the study and were responsible for the data integrity and analysis accuracy. All authors read and approved the final manuscript.

Acknowledgments

Not applicable.

Table 1 The Baseline Characteristics of Participants

PP	Q1(≤36)	Q2(36 to ≤43)	Q3(43 to ≤50)	Q4(>50)	P-value
Participants	39914	47771	43811	51176	
Gender					<0.001
Male	16960 (42.491%)	22739 (47.600%)	24830 (56.675%)	32437 (63.383%)	
Female	22954 (57.509%)	25032 (52.400%)	18981 (43.325%)	18739 (36.617%)	
Age(years)	39.837 ± 9.945	39.905 ± 10.269	40.186 ± 11.236	43.028 ± 14.560	<0.001
Drinking status					
Current-drinker	526 (1.318%)	712 (1.490%)	682 (1.557%)	1004 (1.962%)	
Ex-drinker	3923 (9.829%)	5436 (11.379%)	5777 (13.186%)	7498 (14.651%)	
Never- drinker	35465 (88.854%)	41623 (87.130%)	37352 (85.257%)	42674 (83.387%)	
Smoking status					<0.001
Current-smoker	5468 (13.699%)	7191 (15.053%)	7324 (16.717%)	9441 (18.448%)	
Ex-smoker	1164 (2.916%)	1536 (3.215%)	1707 (3.896%)	2159 (4.219%)	
Never-smoker	33282 (83.384%)	39044 (81.732%)	34780 (79.386%)	39576 (77.333%)	
Family history of diabetes					<0.001
No	38974 (97.645%)	46764 (97.892%)	42922 (97.971%)	50379 (98.443%)	
Yes	940 (2.355%)	1007 (2.108%)	889 (2.029%)	797 (1.557%)	
SBP (mmHg)	104.383 ± 10.737	111.554 ± 10.604	119.000 ± 10.592	131.740 ± 12.760	<0.001
DBP (mmHg)	73.782 ± 10.685	72.461 ± 10.398	73.164 ± 10.347	74.508 ± 10.733	<0.001
BMI (kg/m^2)	22.205 ± 3.119	22.654 ± 3.134	23.100 ± 3.184	23.773 ± 3.358	<0.001
AST(U/L)	21.2 (17, 26.6)	21.5 (17.2, 27)	22 (17.7, 27.8)	23(18.1, 28.7)	<0.001
ALT (U/L)	16 (11.6, 24)	16.6(12, 25.3)	18 (12, 27.4)	19.3(14, 29)	<0.001
HDL-C (mmol/L)	1.394 ± 0.312	1.384 ± 0.310	1.365 ± 0.304	1.351 ± 0.303	<0.001
TG (mmol/L)	0.94 (0.67, 1.40)	0.99 (0.70, 1.47)	1.04 (0.72, 1.55)	1.12 (0.79, 1.69)	<0.001
LDL-C (mmol/L)	2.651 ± 0.656	2.663 ± 0.660	2.685 ± 0.671	2.734 ± 0.690	<0.001
TC (mmol/L)	4.617 ± 0.858	4.632 ± 0.863	4.659 ± 0.880	4.725 ± 0.916	<0.001
BUN (mmol/L)	4.502 ± 1.142	4.538 ± 1.148	4.612 ± 1.156	4.732 ± 1.199	<0.001
SCr (umol/L)	67.116 ± 14.932	68.284 ± 15.134	70.240 ± 15.137	72.093 ± 16.223	<0.001
FPG (mmol/L)	4.691 ± 0.513	4.730 ± 0.497	4.772 ± 0.480	4.849 ± 0.450	<0.001
PP (mmHg)	30.601 ± 3.971	39.093 ± 1.979	45.836 ± 1.986	57.232 ± 6.395	<0.001

Values are n (%) or mean ± SD

PP: pulse pressure, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, ALT alanine aminotransferase, AST aspartate aminotransferase, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TC total cholesterol, TG triglycerides, Scr serum creatinine, BUN blood urea nitrogen, FPG fasting plasma glucose

Table 2 Relationship between PP and incident prediabetes in different models

Variable	Non-adjusted model (HR.,95% CI, P)	Minimally-adjusted model (HR,95% CI, P)	Fully-adjusted model (HR,95% CI, P)	GAM (HR,95% CI, P)
Total	1.025 (1.023, 1.026) <0.00001	1.013 (1.011, 1.014) <0.00001	1.009 (1.007, 1.010) <0.00001	1.008 (1.007, 1.010) <0.00001
PP				
PP (quartile)				
Q1	ref	ref	ref	ref
Q2	1.125 (1.077, 1.176) <0.00001	1.070 (1.024, 1.118) 0.00263	1.043 (0.998, 1.090) 0.06100	1.046 (1.001, 1.093) 0.04505
Q3	1.347 (1.290, 1.407) <0.00001	1.208 (1.156, 1.262) <0.00001	1.131 (1.083, 1.181) <0.00001	1.129 (1.080, 1.179) <0.00001
Q4	1.860 (1.787, 1.935) <0.00001	1.408 (1.352, 1.467) <0.00001	1.246 (1.197, 1.298) <0.00001	1.238 (1.188, 1.291) <0.00001
P for trend	<0.00001	<0.00001	<0.00001	<0.00001
Gender				
Male		ref	ref	
Female		0.777 (0.751, 0.803) <0.00001	0.877 (0.843, 0.913) <0.00001	
Age(years)		1.027 (1.026, 1.028) <0.00001	1.022 (1.021, 1.023) <0.00001	
Drinking status				
Current-drinker		ref	ref	
Ex-drinker		0.965 (0.877, 1.061) 0.45670	1.013 (0.920, 1.114) 0.79930	
Never- drinker		0.911 (0.832, 0.997) 0.04199	1.075 (0.981, 1.178) 0.12156	
Smoking status				
Current-smoker		ref	ref	
Ex-smoker		1.020 (0.948, 1.097) 0.59573	1.021 (0.949, 1.098) 0.57792	
Never-smoker		1.055 (1.016, 1.095) 0.00534	1.023 (0.985, 1.062) 0.24610	
Family history of diabetes				
No		ref	ref	
Yes		1.157 (1.058, 1.265) 0.00142	1.120 (1.024, 1.225) 0.01278	
BMI (kg/m^2)		1.091 (1.086, 1.095) <0.00001	1.060 (1.055, 1.065) <0.00001	
AST(U/L)			0.999 (0.997, 1.000) 0.15002	
ALT (U/L)			1.003 (1.002, 1.004)	

	<0.00001
HDL-C	1.429 (1.353, 1.509)
(mmol/L)	<0.00001
TG (mmol/L)	1.145 (1.129, 1.161)
	<0.00001
LDL-C	1.309 (1.248, 1.373)
(mmol/L)	<0.00001
TC (mmol/L)	0.772 (0.741, 0.803)
	<0.00001
BUN (mmol/L)	0.976 (0.964, 0.988)
	0.00014
SCr (umol/L)	1.003 (1.002, 1.004)
	<0.00001
FPG (mmol/L)	4.613 (4.451, 4.780)
	<0.00001

Crude model: we did not adjust for other covariants.

Minimally-adjusted model: we adjusted for gender, age, family history of diabetes, drinking status, smoking status, and BMI.

Fully-adjusted model: we adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

GAM: All covariates listed in Table 1 were adjusted. However, continuous covariates were adjusted as nonlinearity.

HR, hazard ratios; CI, confidence interval; Ref, reference; GAM, generalized additive mode; PP, pulse pressure.

Table 3 The result of the two-piecewise Cox proportional hazards regression model

Incident prediabetes	HR (95%CI)	P
Fitting model by standard linear regression	1.009 (1.007, 1.010)	<0.0001
Fitting model by two-piecewise Cox proportional hazards regression		
The inflection point of PP (mmHg)	29	
≤29	0.990 (0.977, 1.003)	0.1492
>29	1.009 (1.008, 1.011)	<0.0001
P for the log-likelihood ratio test	0.008	

We adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

HR, hazard ratios; CI, confidence; PP: pulse pressure

Figure 1 Study Population

Figure 2 The nonlinear relationship between PP and incident prediabetes. A nonlinear relationship between PP and incident prediabetes was detected after adjusting for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age.

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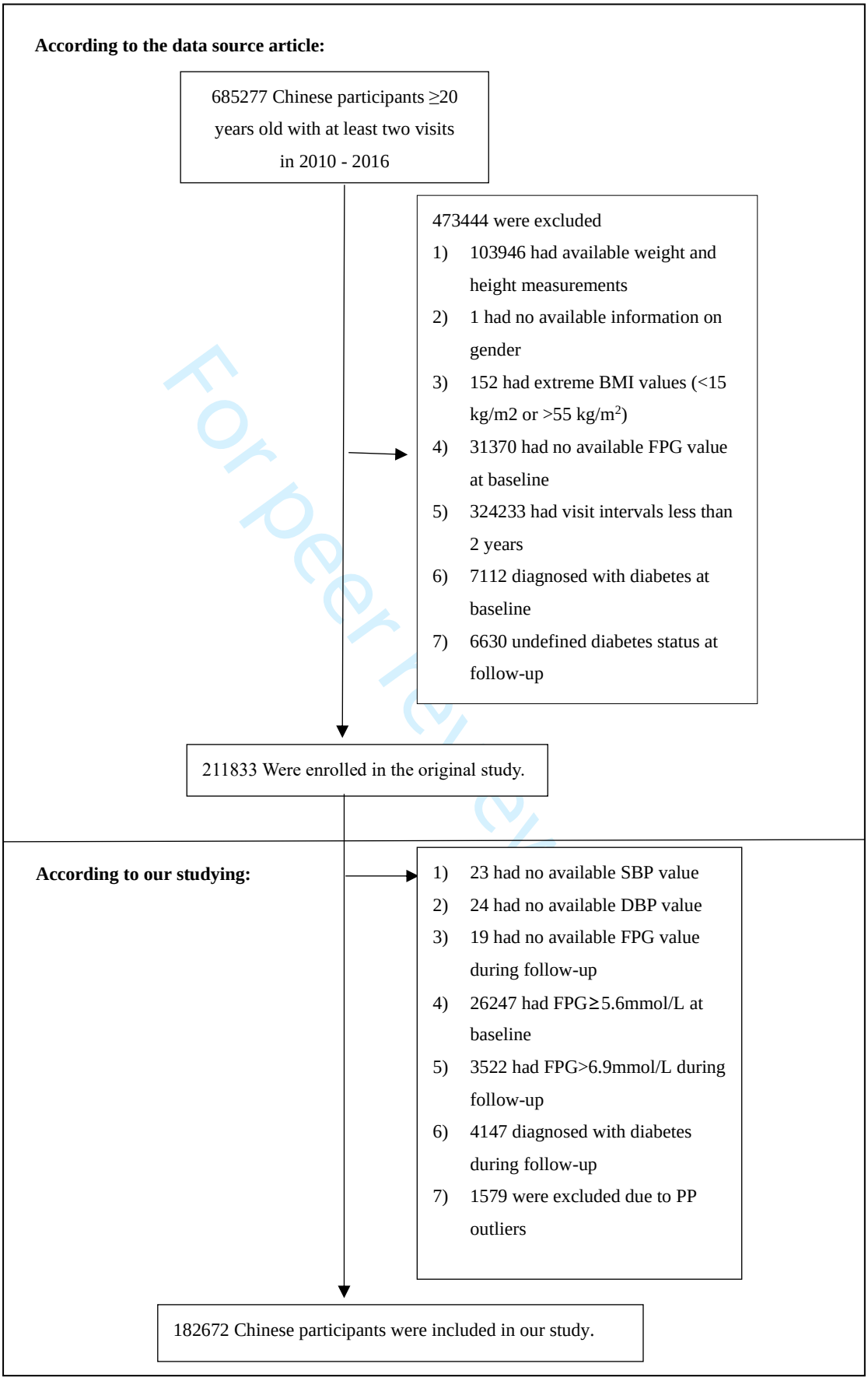

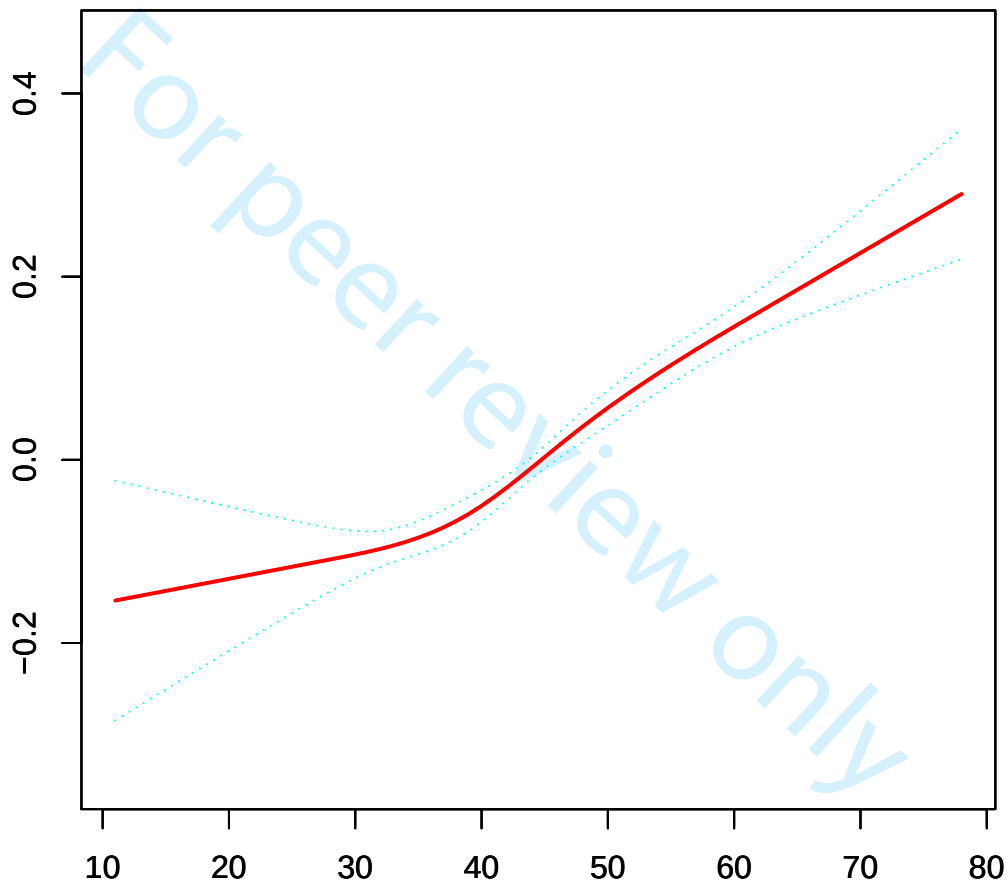

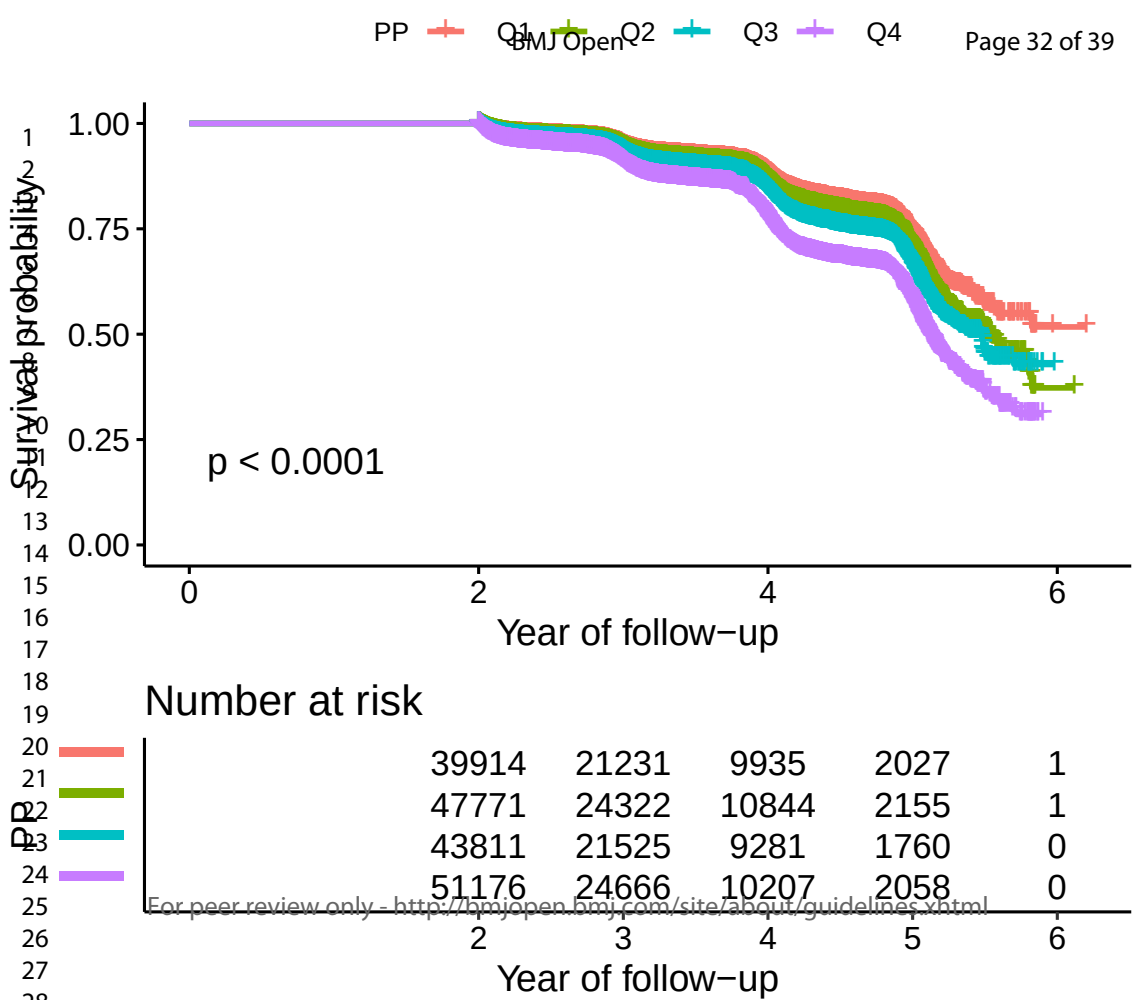

Supplemental Table 1 Incidence rate of incident prediabetes.

PP	Participants (n)	prediabetes events (n)	Cumulative incidence (95%CI) (%)	Per 100,000 person-year
Total	182672	20284	11.10 (10.96–11.25)	3532.68
Q1	39914	3560	8.92(8.64–9.20)	2779.24
Q2	47771	4525	9.47 (9.21–9.73)	2999.95
Q3	43811	4740	10.82 (10.53–11.11)	3470.06
Q4	51176	7459	14.58 (14.27–14.88)	4701.37
P for trend			<0.001	<0.001

PP: pulse pressure, CI: confidence interval

Supplemental Table 2 The results of the univariate analysis

	Statistics	HR (95%CI)	P value
Gender			<0.0001
Male	96966 (53.082%)	ref	
Female	85706 (46.918%)	0.627 (0.609, 0.645)	<0.00001
Age(years)	40.832 ± 11.864	1.033 (1.032, 1.034)	<0.00001
Drinking status			
Current-drinker	2924 (1.601%)	ref	
Ex-drinker	22634 (12.391%)	0.770 (0.701, 0.846)	<0.00001
Never- drinker	157114 (86.009%)	0.607 (0.556, 0.663)	<0.00001
Smoking status			
Current-smoker	29424 (16.108%)	ref	
Ex-smoker	6566 (3.594%)	0.896 (0.834, 0.963)	0.00286
Never-smoker	146682 (80.298%)	0.714 (0.691, 0.739)	<0.00001
Family history of diabetes			0.3503
No	179039 (98.011%)	ref	
Yes	3633 (1.989%)	1.054 (0.965, 1.153) 0.24372	
SBP (mmHg)	117.428 ± 15.208	1.026 (1.025, 1.027)	<0.00001
DBP (mmHg)	73.492 ± 10.572	1.029 (1.028, 1.030)	<0.00001
PP (mmHg)	43.936 ± 10.595	1.025 (1.023, 1.026)	<0.00001
BMI (kg/m2)	22.976 ± 3.259	1.124 (1.120, 1.129)	<0.00001
AST(U/L)	23.591 ± 12.164	1.005 (1.005, 1.006)	<0.00001
ALT (U/L)	23.232 ± 21.734	1.003 (1.003, 1.004)	<0.00001
HDL-C (mmol/L)	1.372 ± 0.307	0.739 (0.707, 0.773)	<0.00001
TG (mmol/L)	1.267 ± 0.934	1.200 (1.192, 1.208)	<0.00001
LDL-C (mmol/L)	2.685 ± 0.671	1.280 (1.256, 1.305)	<0.00001
TC (mmol/L)	4.661 ± 0.882	1.220 (1.202, 1.238)	<0.00001
BUN (mmol/L)	4.602 ± 1.167	1.136 (1.124, 1.149)	<0.00001
SCr (umol/L)	69.565 ± 15.522	1.006 (1.006, 1.007)	<0.00001
FPG (mmol/L)	4.765 ± 0.487	5.711 (5.513, 5.916)	<0.00001

PP: pulse pressure, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, ALT alanine aminotransferase, AST aspartate aminotransferase, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TC total cholesterol, TG triglycerides, Scr serum creatinine, BUN blood urea nitrogen, FPG fasting plasma glucose

Supplemental Table 3 Relationship between PP and prediabetes in different sensitivity analyses

Exposure	Model I (HR,95%CI, P)	Model II (HR,95%CI, P)
PP	1.011 (1.009, 1.013) <0.00001	1.008 (1.007, 1.010) <0.00001
PP (Quintile)		
Q1	Ref	Ref
Q2	1.055 (0.999, 1.115) 0.05494	1.040 (0.993, 1.090) 0.09739
Q3	1.166 (1.104, 1.232) <0.00001	1.123 (1.072, 1.177) <0.00001
Q4	1.310 (1.244, 1.379) <0.00001	1.228 (1.175, 1.285) <0.00001
P for trend	<0.00001	<0.00001

Model I was sensitivity analysis in participants without BMI≥25kg/m^2. We adjusted gender, age, family history of diabetes, drinking status, smoking status, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

Model II was sensitivity analysis in participants without age≥60 years. We adjusted gender, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

HR, hazard ratios; CI, confidence, Ref: reference; PP: pulse pressure

Supplemental Table 4 Variables included age, gender, smoking status, BMI, family history of diabetes, and drinking status interacted with PP

Characteristic	**P-value**
Age	<0.001
Gender	<0.001
BMI	<0.001
Family history of diabetes	<0.001
Smoking status	<0.001
Drinking status	<0.001

Supplemental Table 5 Effect size of PP on prediabetes in prespecified and exploratory subgroups

Characteristic	No of participants	HR (95%CI)	P value	P for interaction
Age, years				0.1335
<60	165813	1.008 (1.006, 1.009)	<0.0001	
≥60	16859	1.010 (1.007, 1.013)	<0.0001	
Gender				0.0002
Male	96966	1.006 (1.004, 1.008)	<0.0001	
Female	85706	1.011 (1.009, 1.013)	<0.0001	
BMI (kg/m^2)				<0.0001
<25	135554	1.012 (1.010, 1.014)	<0.0001	
≥25	47118	1.006 (1.004, 1.008)	<0.0001	
Smoking status				0.0075
Current smoker	29424	1.005 (1.002, 1.008)	0.0002	
Ever smoker	6566	1.007 (1.001, 1.013)	0.0211	
Never smoker	146682	1.010 (1.008, 1.011)	<0.0001	
Drinking status				0.2713
Current drinker	2924	1.014 (1.006, 1.022)	<0.0001	
Ever drinker	22634	1.007 (1.004, 1.010)	<0.0001	
Never drinker	157114	1.009 (1.007, 1.010)	<0.0001	
Family history of diabetes				0.0618
No	179039	1.009 (1.007, 1.010)	<0.0001	
Yes	3633	1.001 (0.992, 1.009)	0.9074	

Note 1: The above model was adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

Note 2: The model is not adjusted for the stratification variable in each case.

Supplemental Table 6 Relationship between PP and the incident prediabetes in pre-imputation data and imputed datasets

Exposure	Pre-imputation	Imputation	P-value
Participants	182672	182672	
Gender			1.000
Male	96966 (53.082%)	96966 (53.082%)	
Female	85706 (46.918%)	85706 (46.918%)	
Age(years)	40.832 ± 11.864	40.832 ± 11.864	1.000
Drinking status			<0.001
Current-drinker	978 (1.932%)	2924 (1.601%)	
Ex-drinker	7340 (14.501%)	22634 (12.391%)	
Never- drinker	42299 (83.567%)	157114 (86.009%)	
Smoking status			<0.001
Current-smoker	9609 (18.984%)	29424 (16.108%)	
Ex-smoker	2104 (4.157%)	6566 (3.594%)	
Never-smoker	38904 (76.860%)	146682 (80.298%)	
Family history of diabetes			1.000
No	179039 (98.011%)	179039 (98.011%)	
Yes	3633 (1.989%)	3633 (1.989%)	
BMI (kg/m^2)	22.976 ± 3.259	22.976 ± 3.259	1.000
AST(U/L)	23.685 ± 12.404	23.591 ± 12.164	0.075
ALT (U/L)	23.219 ± 21.739	23.232 ± 21.734	0.854
HDL-C (mmol/L)	1.378 ± 0.308	1.372 ± 0.307	<0.001
TG (mmol/L)	1.268 ± 0.934	1.267 ± 0.934	0.889
LDL-C (mmol/L)	2.739 ± 0.669	2.685 ± 0.671	<0.001
TC (mmol/L)	4.663 ± 0.883	4.661 ± 0.882	0.630
BUN (mmol/L)	4.604 ± 1.165	4.602 ± 1.167	0.630
SCr (umol/L)	69.628 ± 15.507	69.565 ± 15.522	0.228
FPG (mmol/L)	4.765 ± 0.487	4.765 ± 0.487	1.000

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12 12 12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Nonlinear relationship between pulse pressure and the risk of prediabetes: a secondary retrospective Chinese cohort study

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Nonlinear relationship between pulse pressure and the risk of prediabetes: a secondary retrospective Chinese cohort study

Running title: PP and Pre-DM risk

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Abstract

Objective: Previous research has shown that pulse pressure has a significant role in the start and development of type 2 diabetes mellitus. However, there is little proof that pulse pressure and prediabetes are related. Our study aimed to investigate the relationship between pulse pressure and incident prediabetes in a substantial cohort of Chinese participants.

Design: The 'DATADRYAD' database (www.Datadryad.org) was used to retrieve the data for this secondary retrospective cohort analysis.

Participants: Data from 182672 Chinese individuals who participated in the medical examination program were recorded in this retrospective cohort study between 2010 and 2016 across 32 sites and 11 cities in China.

Setting: Pulse pressure assessed at baseline and incident prediabetes during follow-up were the target-independent and dependent variables. The association between pulse pressure and prediabetes was investigated using Cox proportional hazards regression.

Primary outcome measures: The outcome was incident prediabetes. Impaired fasting glucose levels (fasting blood glucose between 5.6 and 6.9 mmol/L) were used to define prediabetes.

Results: After controlling for confounding variables, pulse pressure was positively correlated with incident prediabetes among Chinese adults (HR: 1.009, 95%CI: 1.007-1.010). Additionally, at a pulse pressure inflection point of 29 mmHg, a nonlinear connection between the pulse pressure and incident prediabetes was discovered. Increased pulse pressure was an independent risk factor for developing prediabetes when pulse pressure was greater than 29 mmHg. However, their association was not significant when pulse pressure was less than 29 mmHg. According to subgroup analyses, females, never smokers, and non-obesity correlated more significantly with

pulse pressure and prediabetes.

Conclusion: We discovered that higher pulse pressure independently correlated with prediabetes risk in this study of Chinese participants. The connection between pulse pressure and incident prediabetes was also nonlinear. High pulse pressure levels were related to a higher risk of prediabetes when pulse pressure was above 29 mmHg.

Article Summary

Article focus

Our study investigated the relationship between PP and incident Pre-DM in a secondary retrospective cohort of Chinese participants.

Strengths and limitations of this study

- Our research leveraged a substantial sample size, drawing participants from multiple centers, thus ensuring a robust representation of the Chinese population.
- We elucidated a nonlinear relationship, marking the pioneering effort to pinpoint the inflection point of PP's impact on Pre-DM.
- Our subgroup analysis allowed us to delve into other potential risk factors within the PP and incident Pre-DM association.
- Our study did not incorporate a 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements, which could potentially lead to an underestimation of the incidence of Pre-DM.

Introduction

Prediabetes (Pre-DM) is intermediate hyperglycemia below the diagnostic cutoff for type 2 diabetes mellitus (T2DM). Patients with Pre-DM have been reported to have a higher risk for cardiovascular disease and nephropathy, indicating that impaired glucose begins to have a pathogenic effect at this early stage of diabetes[1]. The prevalence of Pre-DM is increasing globally with an aging population, urbanization, and changing lifestyles. From 2008 to 2017, the prevalence of Pre-DM in China has climbed from 15.5%[2] to 35.2%[3], creating a significant public health burden. Approximately 70% of subjects with Pre-DM will eventually get T2DM[4]. Numerous studies looked for ways to pinpoint the causes of diabetes and Pre-DM to prevent and cure the disease in its earliest stages.

Pulse pressure (PP) is referred to as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). Clinically, PP is the manifestation of atherosclerosis[5]. Compared to their non-diabetic contemporaries, people with T2DM have greater atherosclerosis, which results in a broad PP[5]. A greater risk of cardiovascular disease (CVD) exists in T2DM patients[6]. In addition, an increase in PP is another risk factor for CVD incidence and positively correlates with mortality[7-9]. Additionally, compared to healthy individuals, prediabetic patients have a greater burden from coronary atherosclerosis[10]. Notably, the atherosclerosis burden began to develop even before T2DM's clinical symptoms[10]. PP was found to be a significant risk factor for T2DM in a recent retrospective cohort investigation of a sizable sample[11]. However, whether prediabetes in Chinese adults is associated with PP is unknown. This study sought to analyze the precise correlation between PP and the likelihood of developing Pre-DM in Chinese participants.

Methods

Data source

Researchers can obtain original research data for free via the Dryad Digital Repository. The Dryad data repository's data on 211833 Chinese persons was downloaded[12]. The current research employed openly available data from a medical examination program as a secondary inquiry. Researchers may use the data for secondary analysis in accordance with the Dryad terms of service without interfering with the interests of the authors.

Study population

The original study was approved by the Rich Healthcare Group Review Board. Hence, ethical approval was not required for this secondary analysis. Each participant conducted under the Rich Healthcare Group Review Board, gave their written informed permission before taking part[12]. In addition, the Declaration of Helsinki was followed during our research. The necessary standards and legislation were followed in the execution of all procedures, including the declarations in the Declarations section.

Individuals were excluded from the investigation under these conditions: (1) diabetes at baseline; (2) diabetes or not defined diabetes status at follow-up; (3) abnormal body mass index (BMI) values (BMI over 55 or less than 15 kg/m²); (4) lacking data on baseline fasting plasma glucose (FPG), FPG at follow-up, height, DBP, gender, weight, and SBP; (5) FPG>6.9mmol/L during follow-up and FPG≥5.6mmol/L at baseline; (6) follow-up interval < 2 years; (7) PP outliers (three standard deviations above or below the mean). Finally, 182672 subjects eventually entered the study. The study's design and participant flow are shown in Figure 1.

Data collection

Trained staff members gathered and compiled all of the data. Data from laboratory inspections were gathered in the original study under uniform conditions using standardized handling procedures. The skilled personnel, including height, blood pressure, body weight, and age, gathered demographic information. Professional trainees without light clothing and shoes measure individuals for weight and height. Weight/Height^2 (kg/m^2) was used to compute BMI. Trained staff members took blood pressure using a standard mercury sphygmomanometer. A Beckman 5800 autoanalyzer was used to measure laboratory data, such as low-density lipoprotein cholesterol (LDL-C), FPG, total cholesterol (TC), aspartate aminotransferase (AST), blood urea nitrogen (BUN), triglyceride (TG), alanine aminotransferase (ALT), serum creatinine (Scr), and high-density lipoprotein cholesterol (HDL-C). SBP (mmHg) - (DBP (mmHg)) were the formulas used to compute PP.

Diagnosis of Pre-DM

Impaired fasting glucose levels (FPG between 5.6 and 6.9 mmol/L) were used to define Pre-DM[13].

Patient and Public Involvement

Given this was a secondary retrospective cohort study, no patient was involved in the study.

Statistical analysis

R software version 3.4.3 and EmpowerStats (R) version 4.0 were used for all statistical analyses.

We initially assessed the baseline data distribution by categorizing it into quartiles based on the PP (Q1$\leq$ 36; 36$<$ Q2 $\leq$43; 43 $<$ Q3 $\leq$50; 50$<$ Q4). Continuous data were reported as medians with interquartile ranges (25th-75th percentile) or means with standard deviations (SD), while

categorical data were expressed as frequencies and percentages. The Kruskal-Wallis H test, chi-square test, and one-way ANOVA were employed to assess disparities between PP groups. The cumulative incidence and terms person-year were used to represent incidence rates[14]. Comparisons of survival and cumulative event rates were done using the Kaplan-Meier method. Using the log-rank test, we also examined the Kaplan-Meier hazard ratios (HR) of unfavorable events [15].

There were 133257 (72.32%), 4240 (2.30%), 1541 (0.84%), 4209 (2.28%), 107684 (58.44%), 82879 (44.98%), 18563 (10.07%), 83382 (45.25%), 9759 (5.30%) and 133257 (72.32%) individuals with missing data for smoking status, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, and drinking status, respectively. The present study employed multiple imputations to handle the missing data of covariants. The imputation model included smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, FPG, sex, family history of diabetes, drinking status, and age. Processes for missing data analysis employ the assumption of missing at random[16].

This analysis assessed each factor's impact on incident Pre-DM using univariate Cox proportional hazards regression models. The multivariate Cox regression analysis also examined the precise connection between the PP and incident Pre-DM. In addition, we created three models (fully-adjusted, minimally-adjusted, and non-adjusted) to evaluate the connection between PP and incident Pre-DM. Suppose the HR is changed by at least 10% after the covariance is included in the model. At this point, the covariance should be adjusted[17].

The current analysis conducted several sensitivity analyses to determine if the findings were trustworthy. We converted PP into a categorical variable based on the quartile. We computed the P for the trend to verify the outcomes of the PP as the continuous variable and test for

nonlinearity. Obesity and older adults were connected to a greater occurrence of Pre-DM. Thus, we excluded individuals with BMI $\geqslant 25 kg/m^2$ or age $\geqslant 60$ years for subsequent sensitivity analyses to examine the connection between PP and Pre-DM risk. Additionally, we incorporated the continuous covariate as a curve to the equation using a generalized additive model (GAM) to confirm the validity of the results. We also calculated E-values to examine the possibility of unmeasured confounding between PP and the risk of prediabetes

We used Cox proportional hazards regression with cubic spline functions and smooth curve fitting to explore the nonlinear relationship between PP and Pre-DM. We first utilized a recursive technique to locate the inflection point if a non-linear relationship was discovered[18]. The recursive algorithm commences with an arbitrary initialization and subsequently undergoes a series of filtering and smoothing steps in order to identify the inflection point accurately. Following this, we construct a two-piece Cox proportional hazards regression model, separately analyzing the data on either side of the inflection point. Ultimately, the study determined the most appropriate model for PP's connection with Pre-DM through log-likelihood ratio analysis.

Subgroup analysis, utilizing the Cox proportional hazard model, was also conducted. Firstly, these variables were selected based on a combination of clinical relevance, literature review, and the availability of data within our cohort. Secondly, the interaction test between these variables and PP was performed before the subgroup analysis. The likelihood ratio test was used to compare models with and without the multiplicative interaction term. Secondly, stratification was performed based on medians or established clinical cut points[19], and variables such as age (<60, ≥60 years) and BMI (<25, ≥25 kg/m^2) were converted into categorical factors. Thirdly, a fully adjusted analysis was performed for each stratum, except for the stratification factor. Ultimately,

the likelihood ratio test was used to determine whether interaction terms existed in models with and without interaction terms[20, 21]. The study adhered to the STROBE statement for all outcomes[17, 22]. Statistical significance was determined by a P-value < 0.05, using two-tailed tests.

Results

Characteristics of individuals

In the current research, 182672 individuals deemed free of Pre-DM at baseline were included. The average age was 40.832 ± 11.864 years, and 53.082% of individuals were male. Twenty thousand two hundred eighty-four individuals eventually got Pre-DM after an average of 3.143 years of follow-up. Table 1 displays comprehensive clinical measurements, biochemical tests, and various parameters. We categorized participants into subgroups based on PP quartiles (Q1≤ 36; 36< Q2 ≤43; 43< Q3≤50; 50< Q4). Compared to the Q1 group, the other groups (Q2 group, Q3 group, Q4 group) had higher ALT, BMI, age, TG, Scr, TC, AST, BUN, LDL-C, and lower HDL-C. Additionally, the Q4 group had a higher proportion of men, smokers, and drinkers.

The incidence rate of Pre-DM

During the follow-up, 20284 individuals developed incident Pre-DM, as outlined in Supplemental Table 1. All people had a prevalence rate of 11.10%. The four PP groups' prevalence rates were 8.92%, 9.47% (9.21%–9.73%), 10.82%, and 14.58%. In addition, the cumulative incidence rate of the overall population and four PP groups were 3532.68, 2779.24, 2999.95, 3470.06, and 4701.37 per 100,000 person-years, respectively. Individuals in the Q2, Q3, and Q4 groups exhibited significantly greater cumulative incidence and prevalence rates of Pre-DM than those in the Q1 group.

The Kaplan-Meier curves for the propensity to survive without Pre-DM are shown in Supplemental Figure 1. There was a significant difference between the four PP groups regarding the likelihood of developing Pre-DM (P<0.001). As PP levels increased, the chance of living without prediabetes steadily dropped. As a result, Pre-DM risk was highest among those in the highest PP categories.

Univariate analysis

Supplemental Table 2 presents the findings of the univariate analysis. DBP, TC, BMI, SBP, FPG, age, TG, SCr, LDL-C, PP, and BUN were correlated with Pre-DM risk. HDL-C exhibits an inverse relationship with Pre-DM risk. Individuals who never drink or smoke also have a lower risk of developing pre-DM. Pre-DM risk was shown to be greater in men than in women.

The results of the connection between PP and Pre-DM

The Cox proportional hazard regression models for the association between PP and Pre-DM are shown in Table 2. In the non-adjusted model, the HR (95%CI) for the relationship between Pre-DM and PP was 1.025 (1.023-1.026). The HR (95%CI) in the minimally-adjusted model was 1.013 (1.011-1.014) after adjusting for smoking status, age, BMI, family history of diabetes, gender, and drinking status. The HR (95%CI) was 1.009 (1.007-1.010) in the fully-adjusted model after controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age. The findings showed that for every 1mmHg rise in PP, the risk of Pre-DM rose by 0.9%.

Sensitivity analyses

We used several sensitivity analyses to evaluate how reliable our results were. PP was changed from a continuous to a categorical variable before being reintroduced into the model. Following

the translation of PP into categorical variables, the trend p was not equal, suggesting a potential nonlinear connection between PP and the chance of developing Pre-DM. Additionally, a GAM added the continuity covariate to the equation. Results for the GAM model showed a positive connection between PP and the probability of developing Pre-DM (HR: 1.008, 95%CI:1.007-1.010) (Table 2).

Besides, the current research excluded participants with BMI<25kg/m^2 for sensitivity analysis. After controlling for confounding factors, we observed a positive association between PP and Pre-DM risk (HR: 1.011, 95%CI: 1.009-1.013) (Supplemental Table 3). Moreover, we considered participants with ages < 60 years for sensitivity studies. After adjusting for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the results showed that PP remained positively correlated with the likelihood of developing Pre-DM (HR: 1.008, 95%CI: 1.007-1.010). (Supplemental Table 3). According to the sensitivity analysis, our findings appeared to be solid.

Additionally, an E-value was computed to assess the vulnerability of the study results to potential unobserved confounding factors. The resulting E-value (1.21) demonstrated a higher level of statistical significance in comparison to the relative risk (1.05) associated with unmeasured confounders and PP. This suggests that the impact of unmeasured or unidentified confounders on the relationship between PP and the occurrence of Pre-DM was negligible.

The analysis of the nonlinear connection

The nonlinear connection between PP and incident Pre-DM is illustrated in Figure 2. After correcting for confounding factors, there was a nonlinear link between PP and incident Pre-DM (Table 3). Based on a two-piecewise Cox proportional hazards regression model, the PP's

inflection point was 29 mmHg (P for log-likelihood ratio test = 0.008). When PP was more than 29 mmHg, PP was strongly linked with incident Pre-DM (HR:1.009, 95%CI: 1.008-1.011, P<0.001). However, their correlation was not significant when PP was less than 29 mmHg (HR: 0.990, 95%CI: 0.977-1.003, P=0.149).

The results of the subgroup analysis

Interaction tests performed before subgroup analyses showed that age, BMI, gender, family history of diabetes, smoking status, and drinking status interacted with PP (P<0.001) (Supplemental Table 4). We selected age, BMI, gender, family history of diabetes, smoking status, and drinking status as stratification variables and examined the changes in their impact sizes (Supplemental Table 5). Age, drinking status, and family history of diabetes had no impact on the correlation between PP and the risk of prediabetes. Females, never smokers, ever smokers, and subjects with BMI<25 kg/m^2 were more likely to be associated with prediabetes risk. Conversely, there was a weaker connection in males, current smokers, and individuals with BMI≥25 kg/m^2.

Discussion

The current study's main goal was to investigate the connection between PP and incident Pre-DM in Chinese participants. The findings demonstrated a correlation between increased PP and a higher risk of prediabetes. The correlation between PP and Pre-DM was also investigated on the left and right sides of the inflection point. PP level and incident prediabetes have a nonlinear relationship. It was found that never-smokers, ever-smokers, females, and individuals with BMI<25 kg/m^2 had a greater correlation between PP and incident Pre-DM.

PP, the arithmetic difference between SBP and DBP, is determined by arterial wall elasticity and is related to all-cause mortality, cardiovascular events, stroke, kidney injury, severe eye

illness, and arterial stiffness[23-28]. In comparison to blood pressure, PP has a better predictive capacity for poor cardiovascular outcomes in people with diabetes, according to several previous pieces of evidence[6, 29]. In addition, some studies found that PP demonstrated strong predictive ability in the homeostatic model assessment of insulin resistance index, diabetes, and metabolic syndrome[30-32]. In a retrospective study involving 211814 Chinese participants, after controlling for BMI, smoking and drinking status, age, TC, gender, family history of diabetes, FPG, TG, and BUN and ALT, Higher PP levels independently connect with increased T2DM risk (HR:1.003, 95%CI:1.001,1.005)[11]. In a longitudinal study involving 12272 Chinese, Zhang L et al.[30] found that high PP in Chinese women may be related to the development of T2DM after adjusting for confounding covariates. In a national cross-sectional study involving 6187 Korean older adults, Kwon YJ et al.[32] discovered a positive association between PP and metabolic syndrome after adjusting for alcohol consumption, smoking, age, regular exercise, and mean arterial blood pressure. In another cross-sectional cohort study that included 38708 rural Chinese participants, compared with the lowest group, the odds ratio (95%CI) of PP in the highest quartile of risk for metabolic syndrome was found to be 1.81 (1.67-1.95) after controlling for confounders[33]. In addition, in a prospective research enrolling 32917 Chinese, the HR (95%CI) for diabetes in the Q3 and Q4 groups were 1.13 (1.04-1.22) and 1.14 (1.05-1.24), respectively, after adjusting for covariates compared to the Q1 group[34]. However, in a multicenter, longitudinal cohort study that included 18619 adults, high PP was not related to an increased risk of diabetes after adjusting for BMI, mean arterial pressure, gender, high-sensitivity C reactive protein, age, exercise, smoking, blood pressure lowering agents, drinking, hyperlipidemia, and family history of diabetes[35]. A retrospective study of 178 individuals with hypertension found that PP was not

associated with the risk of new-onset diabetes after adjusting for potential confounders[36]. This retrospective cohort study involved 182672 Chinese individuals and revealed a higher incidence of prediabetes at increased PP levels. After adjusting for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the results indicated that each unit of the LAP raised the risk of prediabetes by 0.9%. Moreover, sensitivity analysis has demonstrated that this correlation remains observable in Chinese adults with age <60 years or BMI <25 kg/m^2. The efforts mentioned above have demonstrated the consistency of the connection between PP and Pre-DM risk. The findings offered a clinical PP-level intervention guideline to decrease Pre-DM risk.

Few previous studies have investigated the probable curvilinear link between PP and prediabetes. The current study first examined the nonlinear association between PP and prediabetes. After controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the findings revealed that the connection between PP and prediabetes was nonlinear. Based on a two-piecewise Cox proportional hazards regression model, we identified the inflection point of PP as 29 mmHg. When PP levels exceeded 29 mmHg, a 1-unit increase in PP correlated with a 0.9% increase in the hazard ratio (HR) for individuals with Pre-DM (HR: 1.009, 95% CI: 1.008-1.011, P<0.001). However, no significant correlation was observed between PP levels below 29 mmHg and the incident Pre-DM (HR: 0.990, 95% CI: 0.977-1.003, P = 0.149). Elevated PP serves as a valuable indicator for identifying high-risk participants likely to develop Pre-DM during follow-up. Moreover, our analysis revealed that the relationship between PP and the emergence of Pre-DM was more pronounced in never-smokers, ever-smokers, females, and individuals with BMI< 25

kg/m^2. In contrast, this association appeared attenuated in males, current smokers, and individuals with BMI ≥ 25 kg/m^2. Prior research has consistently identified obesity, smoking, and male as contributors to insulin resistance[37, 38], which is a precursor to Pre-DM. We postulated that the attenuated association observed in these subgroups may be attributable to the overriding influence of these risk factors on the pathogenesis of Pre-DM. The direct impact of PP on prediabetes risk may be somewhat eclipsed by the more substantial effects of obesity, active smoking, and the male sex on insulin resistance and subsequent Pre-DM development. This information can remind individuals to adopt healthier lifestyle habits sooner, ultimately improving their outcomes.

The mechanism behind the association between PP and prediabetes is yet unknown. Several explanations currently exist for PP leading to Pre-DM. Firstly, endothelial cell dysfunction may result in microvascular dysfunction[39], which in turn causes dysfunctional glucose metabolism, insulin resistance, poor tissue perfusion, and arterial stiffness[40-42]. Additionally, arterial stiffness may exacerbate microvascular lesions, creating a vicious cycle[43, 44]. Secondly, normal arteries can reduce PP, but arterial stiffness increases blood flow through low-resistance organs (such as the kidney and brain), which will cause organ dysfunction[45]. As a low-resistance, high-blood-flow organ with a mean tissue perfusion of 250–300 ml/min/100g, the pancreas may be negatively impacted by arterial stiffness in terms of its endocrine function.

The current research possesses several notable advantages. Firstly, we delved deeper into the nonlinear relationship between PP and prediabetes. Secondly, we minimized the impact of residual confounding factors through rigorous statistical adjustments. Thirdly, we conducted sensitivity analyses to ensure the robustness of our findings. Lastly, we performed a group analysis to evaluate other potential risk covariates that could affect the link between PP and Pre-DM.

The present study has certain limitations. First, this study is based on a Chinese population, and while it offers valuable insights, the findings might not be directly generalizable to other populations due to genetic, lifestyle, and environmental differences. In the future, we will explore the relationship between PP and prediabetes risk in diverse populations. Second, as our study was a secondary analysis, we cannot guarantee data quality monitoring and variable control. In forthcoming research endeavors, we will endeavor to construct prospective cohort studies with enhanced data quality oversight and variable control, thereby mitigating bias. Third, excluding over 500,000 individuals from a final cohort of 182,672 subjects could have selection bias and implications for generalisability. In the future, we will design prospective studies in a more diverse population to validate our findings. Fourth, prediabetes was defined based on impaired fasting glucose levels in our study. This could potentially lead to underestimation of prediabetes incidence. This is a secondary retrospective study, and the raw data did not provide information regarding 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements. In the future, we will consider designing our study to document more variables, including 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements. Fifth, as with all observational studies, there may be uncontrolled or unmeasured confounding factors, such as diet, exercise, atherosclerosis, the use of antihypertensive medications, and the presence of hypertension, despite controlling for known potential confounders like BMI, TC, LDL-C, AST, ALT, Scr, BUN, and FPG. However, we used the E-value to evaluate the impact of unmeasured confounders and determined it unlikely that they fully explained the results. Sixth, SBP and DBP were only measured at baseline in the original study, and we did not assess how SBP and DBP changed over time. In the future, we will consider designing our own study and documenting more

information, such as diet, exercise, atherosclerosis, antihypertensive medications, the presence of hypertension and changes in blood pressure over time, and then utilizing a GAM model to explore the impact of changes in PP on Pre-DM risk.

Conclusion

This cohort study of the Chinese population shows that PP was inversely and non-linearly associated with the incidence of Pre-DM after adjusting for other confounding factors. High PP levels were related to Pre-DM risk when PP was above 29 mmHg. From a therapeutic standpoint, lowering the PP below the inflection point represents a cost-effective and straightforward approach for the early prevention and intervention of Pre-DM.

Declarations

Ethics approval and consent to participate

The original study followed guidelines outlined by the Helsinki Declaration and was approved by the Rich Healthcare Group Review Board. In addition, the Rich Healthcare Group Review Board has waived informed consent for the current retrospective study. All methods were performed in accordance with the relevant Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article [and/or its supplementary materials].

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Changchun Cao and Yong Han contributed to the study concept and design, researched and interpreted the data, and drafted the manuscript. Haofei Hu, Yongcheng He, and Jiao Luo analyzed the data and reviewed the manuscript. Changchun Cao and Yong Han oversaw the project's progress, contributed to the discussion, and reviewed the manuscript. Haofei Hu, Yongcheng He, and Jiao Luo were the guarantors of this work. As such, they had full access to all data in the study and were responsible for the data integrity and analysis accuracy. All authors read and approved the final manuscript.

Acknowledgments

Not applicable.

Table 1 The Baseline Characteristics of Participants

PP	Q1(≤36)	Q2(36 to ≤43)	Q3(43 to ≤50)	Q4(>50)	P-value
Participants	39914	47771	43811	51176	
Gender					<0.001
Male	16960 (42.491%)	22739 (47.600%)	24830 (56.675%)	32437 (63.383%)	
Female	22954 (57.509%)	25032 (52.400%)	18981 (43.325%)	18739 (36.617%)	
Age(years)	39.837 ± 9.945	39.905 ± 10.269	40.186 ± 11.236	43.028 ± 14.560	<0.001
Drinking status					
Current-drinker	526 (1.318%)	712 (1.490%)	682 (1.557%)	1004 (1.962%)	
Ex-drinker	3923 (9.829%)	5436 (11.379%)	5777 (13.186%)	7498 (14.651%)	
Never- drinker	35465 (88.854%)	41623 (87.130%)	37352 (85.257%)	42674 (83.387%)	
Smoking status					<0.001
Current-smoker	5468 (13.699%)	7191 (15.053%)	7324 (16.717%)	9441 (18.448%)	
Ex-smoker	1164 (2.916%)	1536 (3.215%)	1707 (3.896%)	2159 (4.219%)	
Never-smoker	33282 (83.384%)	39044 (81.732%)	34780 (79.386%)	39576 (77.333%)	
Family history of diabetes					<0.001
No	38974 (97.645%)	46764 (97.892%)	42922 (97.971%)	50379 (98.443%)	
Yes	940 (2.355%)	1007 (2.108%)	889 (2.029%)	797 (1.557%)	
SBP (mmHg)	104.383 ± 10.737	111.554 ± 10.604	119.000 ± 10.592	131.740 ± 12.760	<0.001
DBP (mmHg)	73.782 ± 10.685	72.461 ± 10.398	73.164 ± 10.347	74.508 ± 10.733	<0.001
BMI (kg/m^2)	22.205 ± 3.119	22.654 ± 3.134	23.100 ± 3.184	23.773 ± 3.358	<0.001
AST(U/L)	21.2 (17, 26.6)	21.5 (17.2, 27)	22 (17.7, 27.8)	23(18.1, 28.7)	<0.001
ALT (U/L)	16 (11.6, 24)	16.6(12, 25.3)	18 (12, 27.4)	19.3(14, 29)	<0.001
HDL-C (mmol/L)	1.394 ± 0.312	1.384 ± 0.310	1.365 ± 0.304	1.351 ± 0.303	<0.001
TG (mmol/L)	0.94 (0.67, 1.40)	0.99 (0.70, 1.47)	1.04 (0.72, 1.55)	1.12 (0.79, 1.69)	<0.001
LDL-C (mmol/L)	2.651 ± 0.656	2.663 ± 0.660	2.685 ± 0.671	2.734 ± 0.690	<0.001
TC (mmol/L)	4.617 ± 0.858	4.632 ± 0.863	4.659 ± 0.880	4.725 ± 0.916	<0.001
BUN (mmol/L)	4.502 ± 1.142	4.538 ± 1.148	4.612 ± 1.156	4.732 ± 1.199	<0.001
SCr (umol/L)	67.116 ± 14.932	68.284 ± 15.134	70.240 ± 15.137	72.093 ± 16.223	<0.001
FPG (mmol/L)	4.691 ± 0.513	4.730 ± 0.497	4.772 ± 0.480	4.849 ± 0.450	<0.001
PP (mmHg)	30.601 ± 3.971	39.093 ± 1.979	45.836 ± 1.986	57.232 ± 6.395	<0.001

Values are n (%) or mean ± SD

PP: pulse pressure, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, ALT alanine aminotransferase, AST aspartate aminotransferase, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TC total cholesterol, TG triglycerides, Scr serum creatinine, BUN blood urea nitrogen, FPG fasting plasma glucose

Table 2 Relationship between PP and incident prediabetes in different models

Variable	Non-adjusted model (HR.,95% CI, P)	Minimally-adjusted model (HR,95% CI, P)	Fully-adjusted model (HR,95% CI, P)	GAM (HR,95% CI, P)
Total	1.025 (1.023, 1.026)	1.013 (1.011, 1.014)	1.009 (1.007, 1.010)	1.008 (1.007, 1.010)
PP	<0.001	<0.001	<0.001	<0.001
PP (quartile)				
Q1	ref	ref	ref	ref
Q2	1.125 (1.077, 1.176)	1.070 (1.024, 1.118)	1.043 (0.998, 1.090)	1.046 (1.001, 1.093)
	<0.001	0.003	0.061	0.045
Q3	1.347 (1.290, 1.407)	1.208 (1.156, 1.262)	1.131 (1.083, 1.181)	1.129 (1.080, 1.179)
	<0.001	<0.001	<0.001	<0.001
Q4	1.860 (1.787, 1.935)	1.408 (1.352, 1.467)	1.246 (1.197, 1.298)	1.238 (1.188, 1.291)
	<0.001	<0.001	<0.001	<0.001
P for trend	<0.001	<0.001	<0.001	<0.001
Gender				
Male		ref	ref	
Female		0.777 (0.751, 0.803)	0.877 (0.843, 0.913)	
		<0.001	<0.001	
Age(years)		1.027 (1.026, 1.028)	1.022 (1.021, 1.023)	
		<0.001	<0.001	
Drinking status				
Current-drinker		ref	ref	
Ex-drinker		0.965 (0.877, 1.061)	1.013 (0.920, 1.114)	
		0.457	0.799	
Never- drinker		0.911 (0.832, 0.997)	1.075 (0.981, 1.178)	
		0.042	0.122	
Smoking status				
Current-smoker		ref	ref	
Ex-smoker		1.020 (0.948, 1.097)	1.021 (0.949, 1.098)	
		0.596	0.578	
Never-smoker		1.055 (1.016, 1.095)	1.023 (0.985, 1.062)	
		0.005	0.246	
Family history of diabetes				
No		ref	ref	
Yes		1.157 (1.058, 1.265)	1.120 (1.024, 1.225)	
		0.001	0.013	
BMI (kg/m^2)		1.091 (1.086, 1.095)	1.060 (1.055, 1.065)	
		<0.001	<0.001	
AST(U/L)			0.999 (0.997, 1.000)	
			0.150	
ALT (U/L)			1.003 (1.002, 1.004)	
			<0.001	

HDL-C (mmol/L)	1.429 (1.353, 1.509)
	<0.001
TG (mmol/L)	1.145 (1.129, 1.161)
	<0.001
LDL-C (mmol/L)	1.309 (1.248, 1.373)
	<0.001
TC (mmol/L)	0.772 (0.741, 0.803)
	<0.001
BUN (mmol/L)	0.976 (0.964, 0.988)
	<0.001
SCr (umol/L)	1.003 (1.002, 1.004)
	<0.001
FPG (mmol/L)	4.613 (4.451, 4.780)
	<0.001

Crude model: we did not adjust for other covariants.

Minimally-adjusted model: we adjusted for gender, age, family history of diabetes, drinking status, smoking status, and BMI.

Fully-adjusted model: we adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

GAM: All covariates listed in Table 1 were adjusted. However, continuous covariates were adjusted as nonlinearity.

HR, hazard ratios; CI, confidence interval; Ref, reference; GAM, generalized additive mode; PP, pulse pressure.

Table 3 The result of the two-piecewise Cox proportional hazards regression model

Incident prediabetes	HR (95%CI)	P
Fitting model by standard linear regression	1.009 (1.007, 1.010)	<0.001
Fitting model by two-piecewise Cox proportional hazards regression		
The inflection point of PP (mmHg)	29	
≤29	0.990 (0.977, 1.003)	0.149
>29	1.009 (1.008, 1.011)	<0.001
P for the log-likelihood ratio test	0.008	

We adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

HR, hazard ratios; CI, confidence; PP: pulse pressure

Figure 1 Study Population

Figure 2 The nonlinear relationship between PP and incident prediabetes. A nonlinear relationship between PP and incident prediabetes was detected after adjusting for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age.

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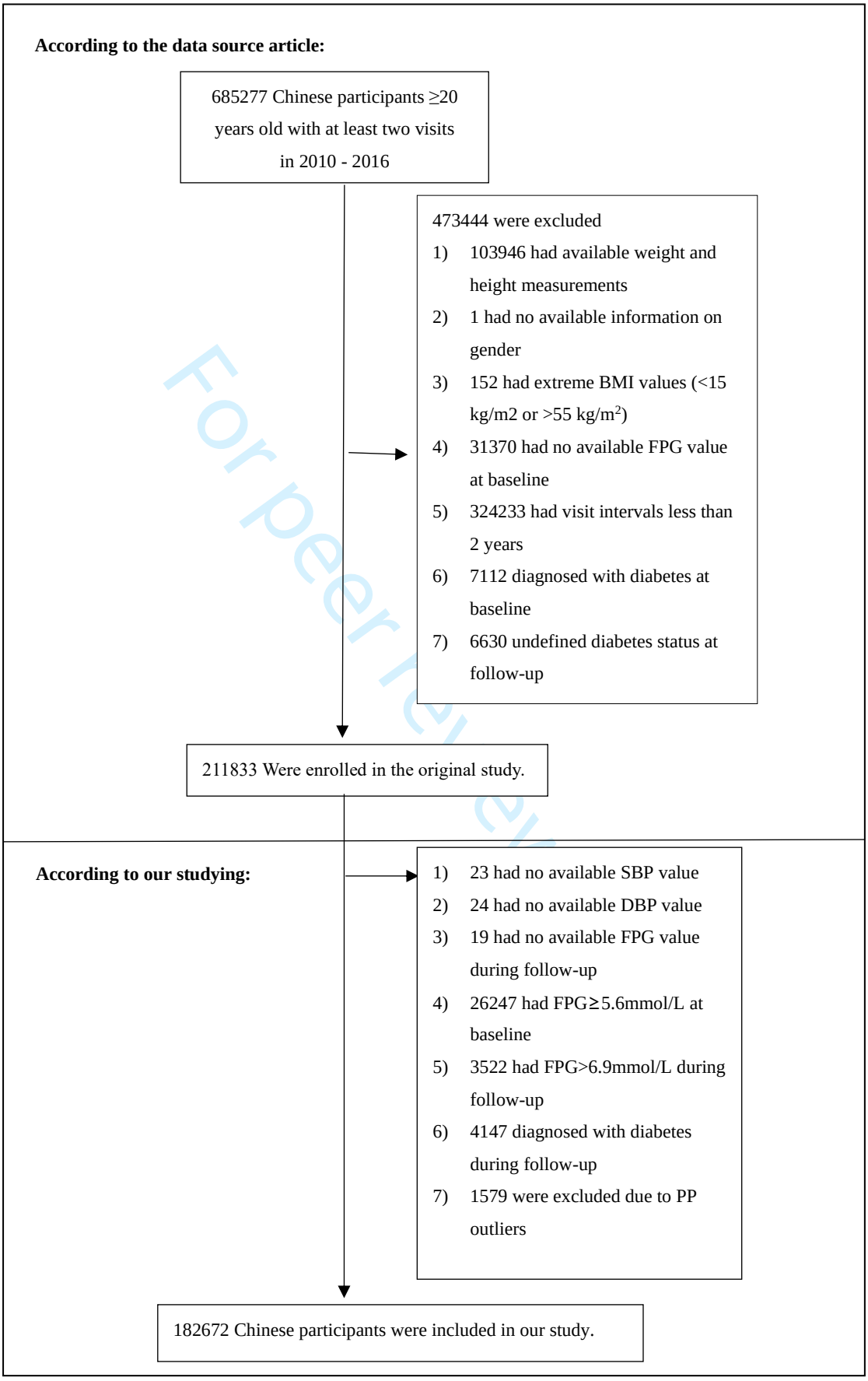
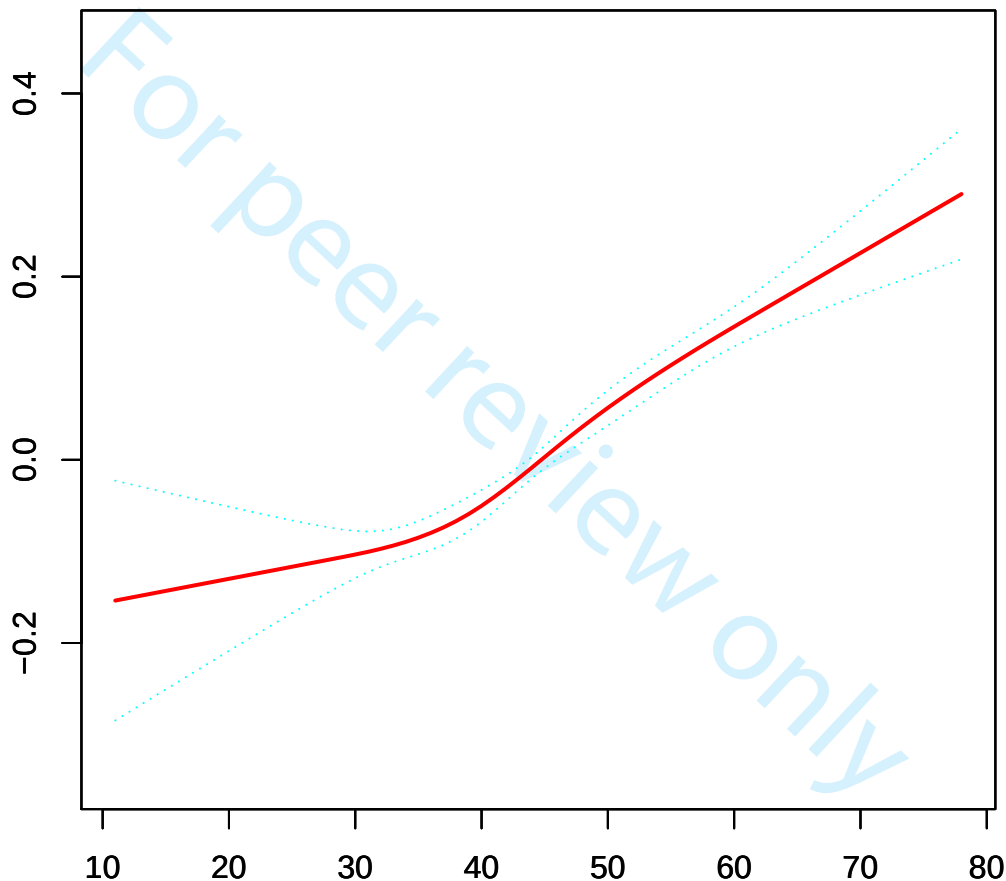




Supplemental Table 1 Incidence rate of incident prediabetes.

PP	Participants (n)	prediabetes events (n)	Cumulative incidence (95%CI) (%)	Per 100,000 person-year
Total	182672	20284	11.10 (10.96–11.25)	3532.68
Q1	39914	3560	8.92(8.64–9.20)	2779.24
Q2	47771	4525	9.47 (9.21–9.73)	2999.95
Q3	43811	4740	10.82 (10.53–11.11)	3470.06
Q4	51176	7459	14.58 (14.27–14.88)	4701.37
P for trend			<0.001	<0.001

PP: pulse pressure, CI: confidence interval

Supplemental Table 2 The results of the univariate analysis

	Statistics	HR (95%CI)	P value
Gender			<0.001
Male	96966 (53.082%)	ref	
Female	85706 (46.918%)	0.627 (0.609, 0.645)	<0.001
Age(years)	40.832 ± 11.864	1.033 (1.032, 1.034)	<0.001
Drinking status			
Current-drinker	2924 (1.601%)	ref	
Ex-drinker	22634 (12.391%)	0.770 (0.701, 0.846)	<0.001
Never- drinker	157114 (86.009%)	0.607 (0.556, 0.663)	<0.001
Smoking status			
Current-smoker	29424 (16.108%)	ref	
Ex-smoker	6566 (3.594%)	0.896 (0.834, 0.963)	0.003
Never-smoker	146682 (80.298%)	0.714 (0.691, 0.739)	<0.001
Family history of diabetes			0.350
No	179039 (98.011%)	ref	
Yes	3633 (1.989%)	1.054 (0.965, 1.153) 0.24372	
SBP (mmHg)	117.428 ± 15.208	1.026 (1.025, 1.027)	<0.001
DBP (mmHg)	73.492 ± 10.572	1.029 (1.028, 1.030)	<0.001
PP (mmHg)	43.936 ± 10.595	1.025 (1.023, 1.026)	<0.001
BMI (kg/m2)	22.976 ± 3.259	1.124 (1.120, 1.129)	<0.001
AST(U/L)	23.591 ± 12.164	1.005 (1.005, 1.006)	<0.001
ALT (U/L)	23.232 ± 21.734	1.003 (1.003, 1.004)	<0.001
HDL-C (mmol/L)	1.372 ± 0.307	0.739 (0.707, 0.773)	<0.001
TG (mmol/L)	1.267 ± 0.934	1.200 (1.192, 1.208)	<0.001
LDL-C (mmol/L)	2.685 ± 0.671	1.280 (1.256, 1.305)	<0.001
TC (mmol/L)	4.661 ± 0.882	1.220 (1.202, 1.238)	<0.001
BUN (mmol/L)	4.602 ± 1.167	1.136 (1.124, 1.149)	<0.001
SCr (umol/L)	69.565 ± 15.522	1.006 (1.006, 1.007)	<0.001
FPG (mmol/L)	4.765 ± 0.487	5.711 (5.513, 5.916)	<0.001

PP: pulse pressure, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, ALT alanine aminotransferase, AST aspartate aminotransferase, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TC total cholesterol, TG triglycerides, Scr serum creatinine, BUN blood urea nitrogen, FPG fasting plasma glucose

Supplemental Table 3 Relationship between PP and prediabetes in different sensitivity analyses

Exposure	Model I (HR,95%CI, P)	Model II (HR,95%CI, P)
PP	1.011 (1.009, 1.013) <0.001	1.008 (1.007, 1.010) <0.001
PP (Quintile)		
Q1	Ref	Ref
Q2	1.055 (0.999, 1.115) 0.055	1.040 (0.993, 1.090) 0.097
Q3	1.166 (1.104, 1.232) <0.001	1.123 (1.072, 1.177) <0.001
Q4	1.310 (1.244, 1.379) <0.001	1.228 (1.175, 1.285) <0.001
P for trend	<0.001	<0.001

Model I was sensitivity analysis in participants without BMI≥25kg/m^2. We adjusted gender, age, family history of diabetes, drinking status, smoking status, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

Model II was sensitivity analysis in participants without age≥60 years. We adjusted gender, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

HR, hazard ratios; CI, confidence, Ref: reference; PP: pulse pressure

Supplemental Table 4 Variables included age, gender, smoking status, BMI, family history of diabetes, and drinking status interacted with PP

Characteristic	**P-value**
Age	<0.001
Gender	<0.001
BMI	<0.001
Family history of diabetes	<0.001
Smoking status	<0.001
Drinking status	<0.001

Supplemental Table 5 Effect size of PP on prediabetes in prespecified and exploratory subgroups

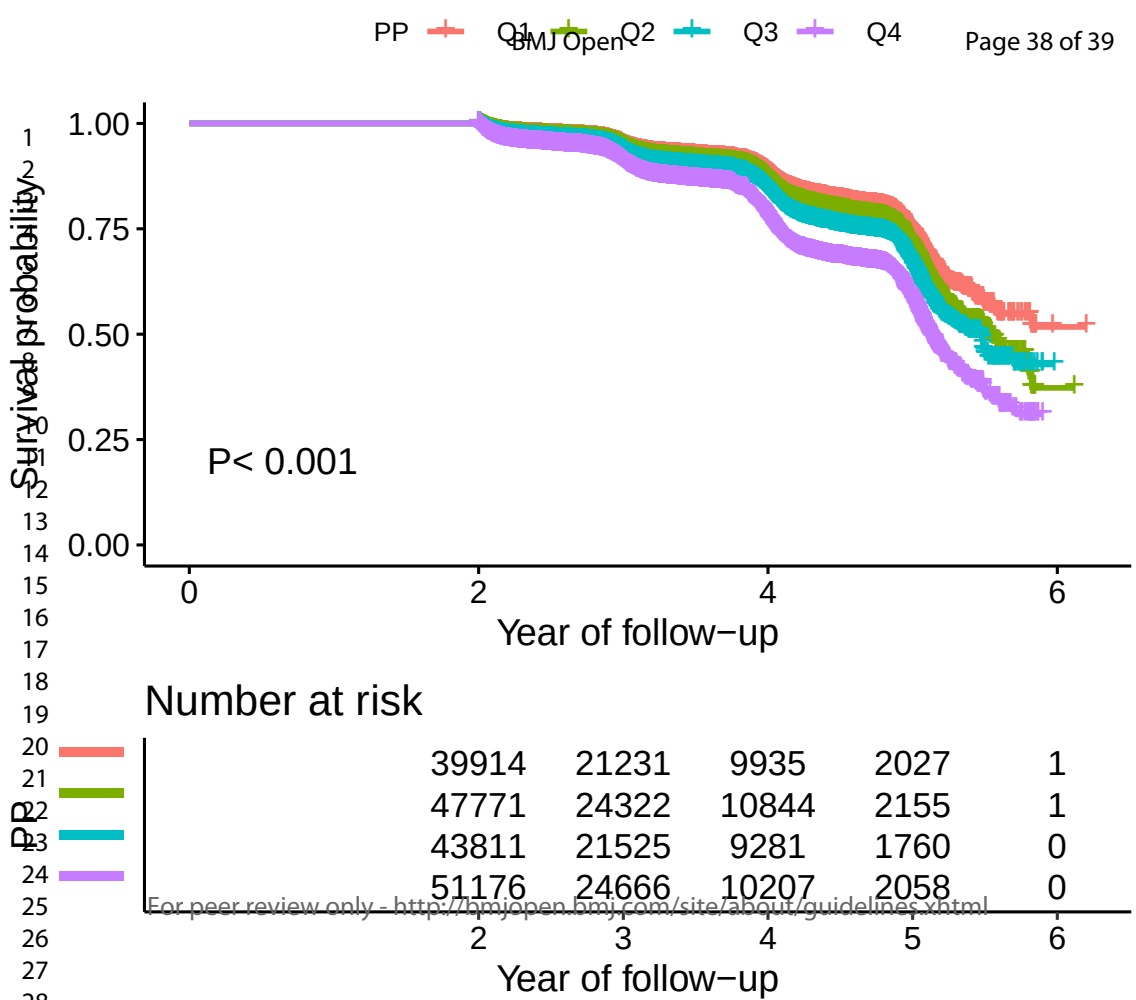
Characteristic	No of participants	HR (95%CI)	P value	P for interaction
Age, years				0.134
<60	165813	1.008 (1.006, 1.009)	<0.001	
≥60	16859	1.010 (1.007, 1.013)	<0.001	
Gender				<0.001
Male	96966	1.006 (1.004, 1.008)	<0.001	
Female	85706	1.011 (1.009, 1.013)	<0.001	
BMI (kg/m^2)				<0.001
<25	135554	1.012 (1.010, 1.014)	<0.001	
≥25	47118	1.006 (1.004, 1.008)	<0.001	
Smoking status				0.008
Current smoker	29424	1.005 (1.002, 1.008)	<0.001	
Ever smoker	6566	1.007 (1.001, 1.013)	0.021	
Never smoker	146682	1.010 (1.008, 1.011)	<0.001	
Drinking status				0.271
Current drinker	2924	1.014 (1.006, 1.022)	<0.001	
Ever drinker	22634	1.007 (1.004, 1.010)	<0.001	
Never drinker	157114	1.009 (1.007, 1.010)	<0.001	
Family history of diabetes				0.062
No	179039	1.009 (1.007, 1.010)	<0.001	
Yes	3633	1.001 (0.992, 1.009)	0.907	

Note 1: The above model was adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.

Note 2: The model is not adjusted for the stratification variable in each case.

Supplemental Table 6 Relationship between PP and the incident prediabetes in pre-imputation data and imputed datasets

Exposure	Pre-imputation	Imputation	P-value
Participants	182672	182672	
Gender			1.000
Male	96966 (53.082%)	96966 (53.082%)	
Female	85706 (46.918%)	85706 (46.918%)	
Age(years)	40.832 ± 11.864	40.832 ± 11.864	1.000
Drinking status			<0.001
Current-drinker	978 (1.932%)	2924 (1.601%)	
Ex-drinker	7340 (14.501%)	22634 (12.391%)	
Never- drinker	42299 (83.567%)	157114 (86.009%)	
Smoking status			<0.001
Current-smoker	9609 (18.984%)	29424 (16.108%)	
Ex-smoker	2104 (4.157%)	6566 (3.594%)	
Never-smoker	38904 (76.860%)	146682 (80.298%)	
Family history of diabetes			1.000
No	179039 (98.011%)	179039 (98.011%)	
Yes	3633 (1.989%)	3633 (1.989%)	
BMI (kg/m^2)	22.976 ± 3.259	22.976 ± 3.259	1.000
AST(U/L)	23.685 ± 12.404	23.591 ± 12.164	0.075
ALT (U/L)	23.219 ± 21.739	23.232 ± 21.734	0.854
HDL-C (mmol/L)	1.378 ± 0.308	1.372 ± 0.307	<0.001
TG (mmol/L)	1.268 ± 0.934	1.267 ± 0.934	0.889
LDL-C (mmol/L)	2.739 ± 0.669	2.685 ± 0.671	<0.001
TC (mmol/L)	4.663 ± 0.883	4.661 ± 0.882	0.630
BUN (mmol/L)	4.604 ± 1.165	4.602 ± 1.167	0.630
SCr (umol/L)	69.628 ± 15.507	69.565 ± 15.522	0.228
FPG (mmol/L)	4.765 ± 0.487	4.765 ± 0.487	1.000



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12 12 12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.