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

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

3 **Running title: PP and Pre-DM risk**

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45 **Abstract**

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

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

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

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

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

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

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4 67 **Conclusion:** We discovered that higher PP independently correlated with Pre-DM risk in this
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6 68 study of Chinese participants. The connection between PP and incident Pre-DM was also
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9 69 nonlinear. High PP levels were related to a higher chance of developing pre-DM when PP was
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11 70 above 29 mmHg.
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4 89 **Article Summary**
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6 90 **Article focus**
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9 91 Our study investigated the relationship between PP and incident Pre-DM in a secondary
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11 92 retrospective cohort of Chinese participants.
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14 93 **Key Messages**
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17 94 We found that elevated PP was independently associated with an increased risk of Pre-DM in our
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19 95 study involving Chinese participants.
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22 96 Higher PP levels were associated with a greater risk of developing Pre-DM when PP exceeded 29
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24 97 mmHg.
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27 98 Further investigation is needed to understand PP's impact on the incident Pre-DM.
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30 99 **Strengths and limitations of this study**
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32 100 Our research leveraged a substantial sample size, drawing participants from multiple centers, thus
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34 101 ensuring a robust representation of the Chinese population.
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37 102 We elucidated a nonlinear relationship, marking the pioneering effort to pinpoint the inflection
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39 103 point of PP's impact on Pre-DM.
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42 104 Our subgroup analysis allowed us to delve into other potential risk factors within the PP and
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44 105 incident Pre-DM association.
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48 106 Our study did not incorporate a 2-hour oral glucose tolerance test or glycosylated hemoglobin
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50 107 level measurements, which could potentially lead to an underestimation of the incidence of
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52 108 Pre-DM.
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111 **Introduction**

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

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

133 **Methods**

134 **Data source**

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

140 **Study population**

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

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

152 **Data collection**

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

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4 155 procedures. The skilled personnel, including height, blood pressure, body weight, and age,
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6 156 gathered demographic information. Professional trainees without light clothing and shoes measure
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9 157 individuals for weight and height. Weight/Height² (kg/m²) was used to compute BMI. Trained
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12 158 staff members took blood pressure using a standard mercury sphygmomanometer. A Beckman
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14 159 5800 autoanalyzer was used to measure laboratory data, such as low-density lipoprotein
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17 160 cholesterol (LDL-C), FPG, total cholesterol (TC), aspartate aminotransferase (AST), blood urea
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19 161 nitrogen (BUN), triglyceride (TG), alanine aminotransferase (ALT), serum creatinine (Scr), and
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22 162 high-density lipoprotein cholesterol (HDL-C). SBP (mmHg) - (DBP (mmHg)) were the formulas
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25 163 used to compute PP.

26 27 164 **Diagnosis of Pre-DM**

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30 165 Impaired fasting glucose levels (FPG between 5.6 and 6.9 mmol/L) were used to define
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33 166 Pre-DM[13].

34 35 167 **Statistical analysis**

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38 168 R software version 3.4.3 and EmpowerStats (R) version 4.0 were used for all statistical
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41 169 analyses.

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43 170 We initially assessed the baseline data distribution by categorizing it into quartiles based on the
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46 171 PP ($Q1 \leq 36$; $36 < Q2 \leq 43$; $43 < Q3 \leq 50$; $50 < Q4$). Continuous data were reported as medians with
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49 172 interquartile ranges (25th-75th percentile) or means with standard deviations (SD), while
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52 173 categorical data were expressed as frequencies and percentages. The Kruskal-Wallis H test,
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55 174 chi-square test, and one-way ANOVA were employed to assess disparities between PP groups.
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58 175 The cumulative incidence and terms person-year were used to represent incidence rates[14].
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60 176 Comparisons of survival and cumulative event rates were done using the Kaplan-Meier method.

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4 177 Using the log-rank test, we also examined the Kaplan-Meier hazard ratios (HR) of unfavorable
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6 178 events [15].
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9 179 There were 133257 (72.32%), 4240 (2.30%), 1541 (0.84%), 4209 (2.28%), 107684 (58.44%),
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11 180 82879 (44.98%), 18563 (10.07%), 83382 (45.25%), 9759 (5.30%) and 133257 (72.32%)
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14 181 individuals with missing data for smoking status, TG, ALT, TC, AST, LDL-C, BUN, HDL-C,
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17 182 SCr, and drinking status, respectively. The present study employed multiple imputations to handle
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20 183 the missing data of covariants. The imputation model included smoking status, BMI, TG, ALT,
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22 184 TC, AST, LDL-C, BUN, HDL-C, SCr, FPG, sex, family history of diabetes, drinking status, and
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25 185 age. Processes for missing data analysis employ the assumption of missing at random[16].
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27 186 This analysis assessed each factor's impact on incident Pre-DM using univariate Cox
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30 187 proportional hazards regression models. The multivariate Cox regression analysis also examined
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33 188 the precise connection between the PP and incident Pre-DM. In addition, we created three models
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36 189 (fully-adjusted, minimally-adjusted, and non-adjusted) to evaluate the connection between PP and
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39 190 incident Pre-DM. Suppose the HR is changed by at least 10% after the covariance is included in
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42 191 the model. At this point, the covariance should be adjusted[17].
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44 192 The current analysis conducted several sensitivity analyses to determine if the findings were
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47 193 trustworthy. We converted PP into a categorical variable based on the quartile. We computed the
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50 194 P for the trend to verify the outcomes of the PP as the continuous variable and test for
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53 195 nonlinearity. Obesity and older adults were connected to a greater occurrence of Pre-DM. Thus,
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56 196 we excluded individuals with BMI $\geq 25\text{kg/m}^2$ or age ≥ 60 years for subsequent sensitivity
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59 197 analyses to examine the connection between PP and Pre-DM risk. Additionally, we incorporated
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198 the continuous covariate as a curve to the equation using a generalized additive model (GAM) to

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4 199 confirm the validity of the results.
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6 200 Considering PP is a continuous variable, we investigated potential nonlinear correlations
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9 201 between PP and Pre-DM using the Cox proportional hazards regression with cubic spline
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11 202 functions and smooth curve fitting. If the relationship proved nonlinear, a two-piecewise Cox
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13 203 proportional hazards regression model was applied to pinpoint the inflection point[18]. The study
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15 204 determined the most appropriate model for PP's connection with Pre-DM through log-likelihood
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17 205 ratio analysis.
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22 206 Subgroup analysis, utilizing the Cox proportional hazard model, was also conducted. Subgroup
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24 207 variables included smoking status, age, BMI, family history of diabetes, gender, and drinking
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26 208 status. Stratification was performed based on medians or established clinical cut points[19], and
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28 209 variables such as age (<60, ≥60 years) and BMI (<25, ≥25 kg/m²) were converted into categorical
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30 210 factors. Each stratum underwent a thoroughly adjusted analysis, except for the stratification factor.
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32 211 The likelihood ratio tests were conducted to ascertain subgroup interactions[20, 21]. The study
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34 212 adhered to the STROBE statement for all outcomes[17, 22]. Statistical significance was
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36 213 determined by a P-value < 0.05, using two-tailed tests.
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43 214 **Results**

44 215 **Characteristics of individuals**

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47 216 In the current research, 182672 individuals deemed free of Pre-DM at baseline were included.
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49 217 The average age was 40.832 ± 11.864 years, and 53.082% of individuals were male. Twenty
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51 218 thousand two hundred eighty-four individuals eventually got Pre-DM after an average of 3.143
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53 219 years of follow-up. Table 1 displays comprehensive clinical measurements, biochemical tests, and
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55 220 various parameters. We categorized participants into subgroups based on PP quartiles (Q1≤36;
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4 221 36<Q2≤43; 43<Q3≤50; 50<Q4). Compared to the Q1 group, the other groups (Q2 group, Q3
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6 222 group, Q4 group) had higher ALT, BMI, age, TG, Scr, TC, AST, BUN, LDL-C, and lower
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9 223 HDL-C. Additionally, the Q4 group had a higher proportion of men, smokers, and drinkers.

10 11 224 **The incidence rate of Pre-DM**

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14 225 During the follow-up, 20284 individuals developed incident Pre-DM, as outlined in
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17 226 Supplemental Table 1. All people had a prevalence rate of 11.10%. The four PP groups'
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19 227 prevalence rates were 8.92%, 9.47% (9.21%–9.73%), 10.82%, and 14.58%. In addition, the
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22 228 cumulative incidence rate of the overall population and four PP groups were 3532.68, 2779.24,
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25 229 2999.95, 3470.06, and 4701.37 per 100,000 person-years, respectively. Individuals in the Q2, Q3,
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28 230 and Q4 groups exhibited significantly greater cumulative incidence and prevalence rates of
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30 231 Pre-DM than those in the Q1 group.

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32 232 The Kaplan-Meier curves for the propensity to survive without Pre-DM are shown in
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35 233 Supplemental Figure 1. There was a significant difference between the four PP groups regarding
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38 234 the likelihood of developing Pre-DM (P 0.0001). As PP levels increased, the chance of living
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41 235 without prediabetes steadily dropped. As a result, Pre-DM risk was highest among those in the
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44 236 highest PP categories.

45 237 **Univariate analysis**

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48 238 Supplemental Table 2 presents the findings of the univariate analysis. DBP, TC, BMI, SBP,
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51 239 FPG, age, TG, SCr, LDL-C, PP, and BUN were correlated with Pre-DM risk. HDL-C exhibits an
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54 240 inverse relationship with Pre-DM risk. Individuals who never drink or smoke also have a lower
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57 241 risk of developing pre-DM. Pre-DM risk was shown to be greater in men than in women.

58 242 **The results of the connection between PP and Pre-DM**

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4 243 The Cox proportional hazard regression models for the association between PP and Pre-DM are
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6 244 shown in Table 2. In the non-adjusted model, the HR (95%CI) for the relationship between
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9 245 Pre-DM and PP was 1.025 (1.023-1.026). The HR (95%CI) in the minimally-adjusted model was
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11 246 1.013 (1.011-1.014) after adjusting for smoking status, age, BMI, family history of diabetes,
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14 247 gender, and drinking status. The HR (95%CI) was 1.009 (1.007-1.010) in the fully-adjusted model
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17 248 after controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex,
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19 249 FPG, family history of diabetes, drinking status, and age. The findings showed that for every
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22 250 1mmHg rise in PP, the risk of Pre-DM rose by 0.9%.

251 **Sensitivity analyses**

252 We used several sensitivity analyses to evaluate how reliable our results were. PP was changed
253 from a continuous to a categorical variable before being reintroduced into the model. Following
254 the translation of PP into categorical variables, the trend p was not equal, suggesting a potential
255 nonlinear connection between PP and the chance of developing Pre-DM. Additionally, a GAM
256 added the continuity covariate to the equation. Results for the GAM model showed a positive
257 connection between PP and the probability of developing Pre-DM (HR: 1.008,
258 95%CI:1.007-1.010) (Table 2).

259 Besides, the current research excluded participants with BMI<25kg/m² for sensitivity analysis.
260 After controlling for confounding factors, we observed a positive association between PP and
261 Pre-DM risk (HR: 1.011, 95%CI: 1.009-1.013) (Supplemental Table 3). Moreover, we considered
262 participants with ages < 60 years for sensitivity studies. After adjusting for smoking status, BMI,
263 TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking
264 status, and age, the results showed that PP remained positively correlated with the likelihood of

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4 265 developing Pre-DM (HR: 1.008, 95%CI: 1.007-1.010). (Supplemental Table 3). According to the
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6 266 sensitivity analysis, our findings appeared to be solid.
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9 267 **The analysis of the nonlinear connection**

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11 268 The nonlinear connection between PP and incident Pre-DM is illustrated in Figure 2. After
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13 269 correcting for confounding factors, there was a nonlinear link between PP and incident Pre-DM
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15 270 (Table 3). Based on a two-piecewise Cox proportional hazards regression model, the PP's
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17 271 inflection point was 29 mmHg (P for log-likelihood ratio test = 0.008). When PP was more than
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19 272 29 mmHg, PP was strongly linked with incident Pre-DM (HR:1.009, 95%CI: 1.008-1.011,
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21 273 P<0.0001). However, their correlation was not significant when PP was less than 29 mmHg (HR:
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23 274 0.990, 95%CI: 0.977-1.003, P=0.1492).
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30 275 **The results of the subgroup analysis**

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32 276 In our investigation, subgroup analysis was used to examine other risk variables that could have
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34 277 altered the relationship between PP and incident prediabetes. We selected age, BMI, gender,
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36 278 family history of diabetes, smoking status, and drinking status as stratification variables and
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38 279 examined the changes in their impact sizes (Supplemental Table 4). Age, drinking status, and
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40 280 family history of diabetes had no impact on the correlation between PP and the risk of prediabetes.
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42 281 Females, never smokers, ever smokers, and subjects with BMI<25 kg/m² were more likely to be
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44 282 associated with prediabetes risk. Conversely, there was a weaker connection in males, current
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46 283 smokers, and individuals with BMI≥25 kg/m².
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53 284 **Discussion**

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55 285 The current study's main goal was to investigate the connection between PP and incident
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57 286 Pre-DM in Chinese participants. The findings demonstrated a correlation between increased PP
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4 287 and a higher risk of prediabetes. The correlation between PP and Pre-DM was also investigated on
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6 288 the left and right sides of the inflection point. PP level and incident prediabetes have a nonlinear
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9 289 relationship. It was found that never-smokers, ever-smokers, females, and individuals with
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11 290 BMI<25 kg/m² had a greater correlation between PP and incident Pre-DM.
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14 291 PP, the arithmetic difference between SBP and DBP, is determined by arterial wall elasticity
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16 292 and is related to all-cause mortality, cardiovascular events, stroke, kidney injury, severe eye
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19 293 illness, and arterial stiffness[23-28]. In comparison to blood pressure, PP has a better predictive
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22 294 capacity for poor cardiovascular outcomes in people with diabetes, according to several previous
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25 295 pieces of evidence[6, 29]. In addition, some studies found that PP demonstrated strong predictive
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28 296 ability in the homeostatic model assessment of insulin resistance index, diabetes, and metabolic
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30 297 syndrome[30-32]. In a retrospective study involving 211814 Chinese participants, after controlling
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33 298 for BMI, smoking and drinking status, age, TC, gender, family history of diabetes, FPG, TG, and
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35 299 BUN and ALT, Higher PP levels independently connect with increased T2DM risk (HR:1.003,
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37 300 95%CI:1.001,1.005)[11]. In a longitudinal study involving 12272 Chinese, Zhang L et al.[30]
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40 301 found that high PP in Chinese women may be related to the development of T2DM after adjusting
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43 302 for confounding covariates. In a national cross-sectional study involving 6187 Korean older
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45 303 adults, Kwon YJ et al.[32] discovered a positive association between PP and metabolic syndrome
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48 304 after adjusting for alcohol consumption, smoking, age, regular exercise, and mean arterial blood
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51 305 pressure. In another cross-sectional cohort study that included 38708 rural Chinese participants,
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53 306 compared with the lowest group, the odds ratio (95%CI) of PP in the highest quartile of risk for
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56 307 metabolic syndrome was found to be 1.81 (1.67-1.95) after controlling for confounders[33]. In
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59 308 addition, in a prospective research enrolling 32917 Chinese, the HR (95%CI) for diabetes in the
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4 309 Q3 and Q4 groups were 1.13 (1.04-1.22) and 1.14 (1.05-1.24), respectively, after adjusting for
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6 310 covariates compared to the Q1 group[34]. However, in a multicenter, longitudinal cohort study
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8 311 that included 18619 adults, high PP was not related to an increased risk of diabetes after adjusting
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10 312 for BMI, mean arterial pressure, gender, high-sensitivity C reactive protein, age, exercise,
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12 313 smoking, blood pressure lowering agents, drinking, hyperlipidemia, and family history of
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14 314 diabetes[35]. A retrospective study of 178 individuals with hypertension found that PP was not
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16 315 associated with the risk of new-onset diabetes after adjusting for potential confounders[36]. This
17
18 316 retrospective cohort study involved 182672 Chinese individuals and revealed a higher incidence of
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20 317 prediabetes at increased PP levels. After adjusting for smoking status, BMI, TG, ALT, TC, AST,
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22 318 LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the
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24 319 results indicated that each unit of the LAP raised the risk of prediabetes by 0.9%. Moreover,
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26 320 sensitivity analysis has demonstrated that this correlation remains observable in Chinese adults
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28 321 with age <60 years or BMI <25 kg/m². The efforts mentioned above have demonstrated the
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30 322 consistency of the connection between PP and Pre-DM risk. The findings offered a clinical
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32 323 PP-level intervention guideline to decrease Pre-DM risk.

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43 324 Few previous studies have investigated the probable curvilinear link between PP and
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45 325 prediabetes. The current study first examined the nonlinear association between PP and
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47 326 prediabetes. After controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN,
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49 327 HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the findings revealed
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51 328 that the connection between PP and prediabetes was nonlinear. Based on a two-piecewise Cox
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53 329 proportional hazards regression model, we identified the inflection point of PP as 29 mmHg.
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56 330 When PP levels exceeded 29 mmHg, a 1-unit increase in PP correlated with a 0.9% increase in the
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4 331 hazard ratio (HR) for individuals with Pre-DM (HR: 1.009, 95% CI: 1.008-1.011, P<0.0001).
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6 332 However, no significant correlation was observed between PP levels below 29 mmHg and the
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9 333 incident Pre-DM (HR: 0.990, 95% CI: 0.977-1.003, P = 0.1492). Elevated PP serves as a valuable
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11 334 indicator for identifying high-risk participants likely to develop Pre-DM during follow-up. This
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14 335 information can remind individuals to adopt healthier lifestyle habits sooner, ultimately improving
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17 336 their outcomes.

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19 337 The mechanism behind the association between PP and prediabetes is yet unknown. Several
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21 338 explanations currently exist for PP leading to Pre-DM. Firstly, endothelial cell dysfunction may
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24 339 result in microvascular dysfunction[37], which in turn causes dysfunctional glucose metabolism,
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27 340 insulin resistance, poor tissue perfusion, and arterial stiffness[38-40]. Additionally, arterial
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30 341 stiffness may exacerbate microvascular lesions, creating a vicious cycle[41, 42]. Secondly, normal
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33 342 arteries can reduce PP, but arterial stiffness increases blood flow through low-resistance organs
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36 343 (such as the kidney and brain), which will cause organ dysfunction[43]. As a low-resistance,
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38 344 high-blood-flow organ with a mean tissue perfusion of 250–300 ml/min/100g, the pancreas may
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41 345 be negatively impacted by arterial stiffness in terms of its endocrine function.

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43 346 The current research possesses several notable advantages. Firstly, we delved deeper into the
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46 347 nonlinear relationship between PP and prediabetes. Secondly, we minimized the impact of residual
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49 348 confounding factors through rigorous statistical adjustments. Thirdly, we conducted sensitivity
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52 349 analyses to ensure the robustness of our findings. Lastly, we performed a group analysis to
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55 350 evaluate other potential risk covariates that could affect the link between PP and Pre-DM.

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57 351 The present study has certain limitations. First, because we used FPG levels to diagnose
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60 352 Pre-DM in this investigation, we might have overlooked some new cases of Pre-DM. Second, our

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4 353 database lacks information on atherosclerosis, the use of antihypertensive medications, and the
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7 354 presence of hypertension. As a result, a sub-analysis based on the presence or absence of
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9 355 hypertension or the use of antihypertensive drugs was not possible. Third, SBP and DBP were
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11 356 only measured at baseline in the original study, and we did not assess how SBP and DBP changed
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14 357 over time. Future iterations of our investigation may incorporate additional confounding variables,
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17 358 such as variations in SBP and DBP during follow-up, hypertension, and antihypertensive
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19 359 medications. Consequently, we may consider utilizing a GAM model to explore the impact of
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22 360 changes in PP on future Pre-DM risk.

361 **Conclusion**

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

368 **Declarations**

369 **Ethics approval and consent to participate**

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

373 **Consent for publication**

374 Not applicable.

375 **Availability of data and materials**

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

378 **Competing interests**

379 The authors declare that they have no competing interests.

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382 **Author contributions**

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

390 **Acknowledgments**

391 Not applicable.

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397 **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	
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	

398 Values are n (%) or mean ± SD

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

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410 **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) <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

411 Crude model: we did not adjust for other covariants.

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

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

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

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

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441 **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	

442 We adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST,

443 ALT, SCr, BUN, and FPG.

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

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4 472 **Figure 1** Study Population
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6 473 **Figure 2** The nonlinear relationship between PP and incident prediabetes. A nonlinear
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9 474 relationship between PP and incident prediabetes was detected after adjusting for
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12 475 smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG,
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14 476 family history of diabetes, drinking status, and age.
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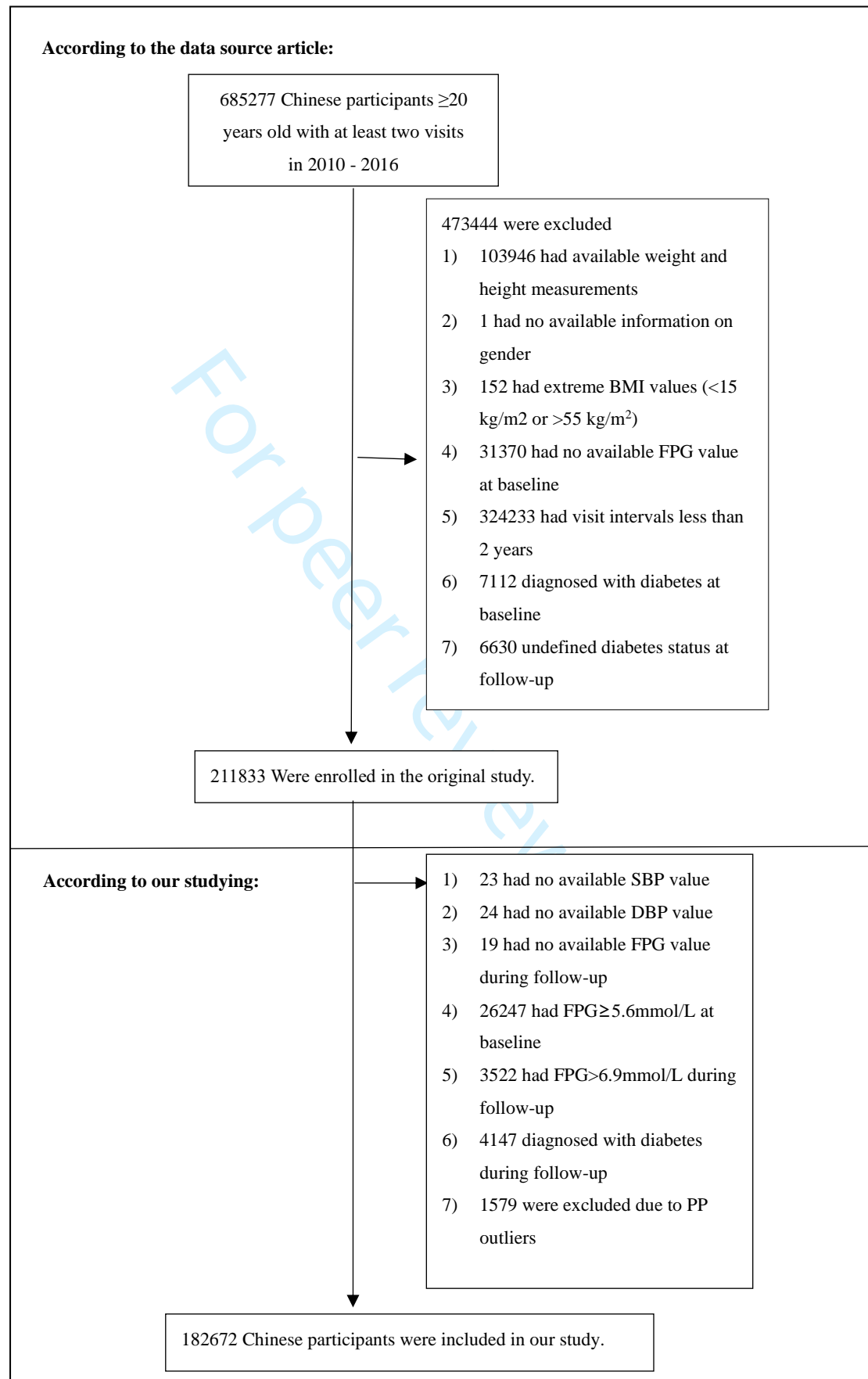
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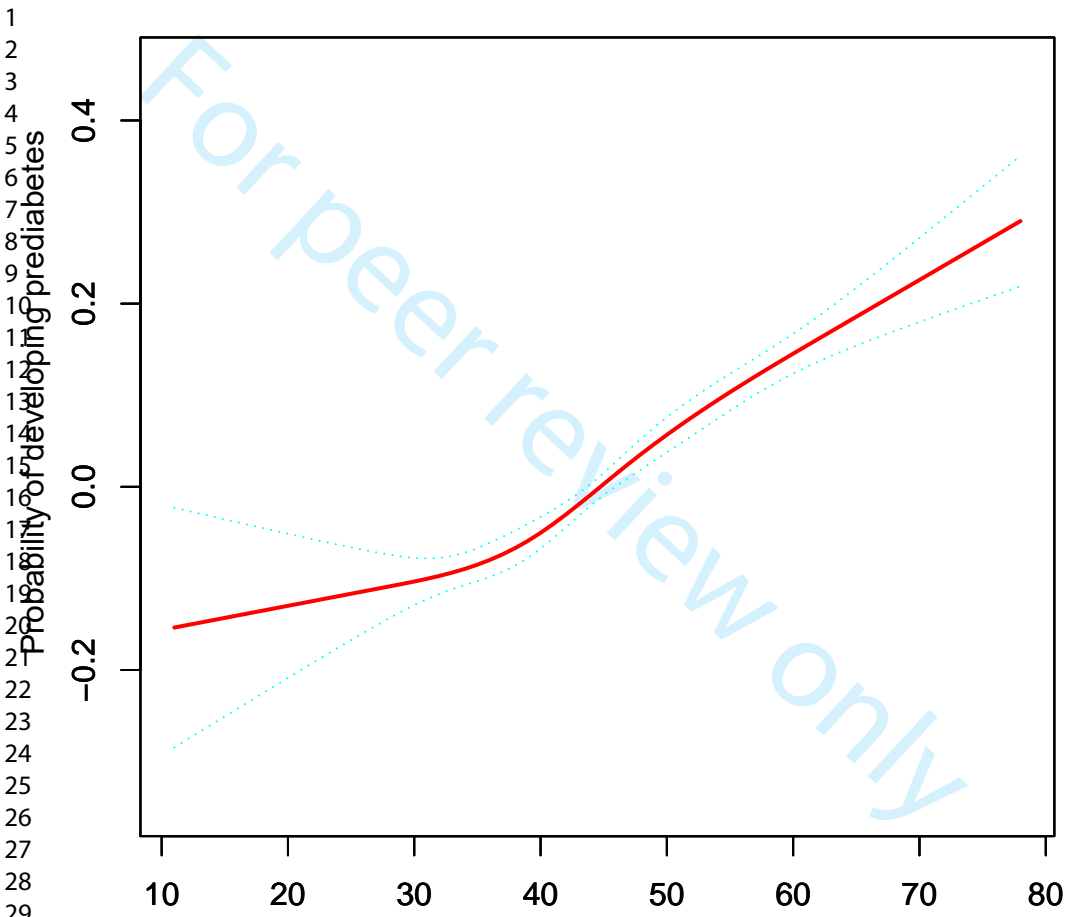
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Supplemental Table 1 Incidence rate of incident prediabetes.

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/m ²)	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 \geq 25kg/m². 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 \geq 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

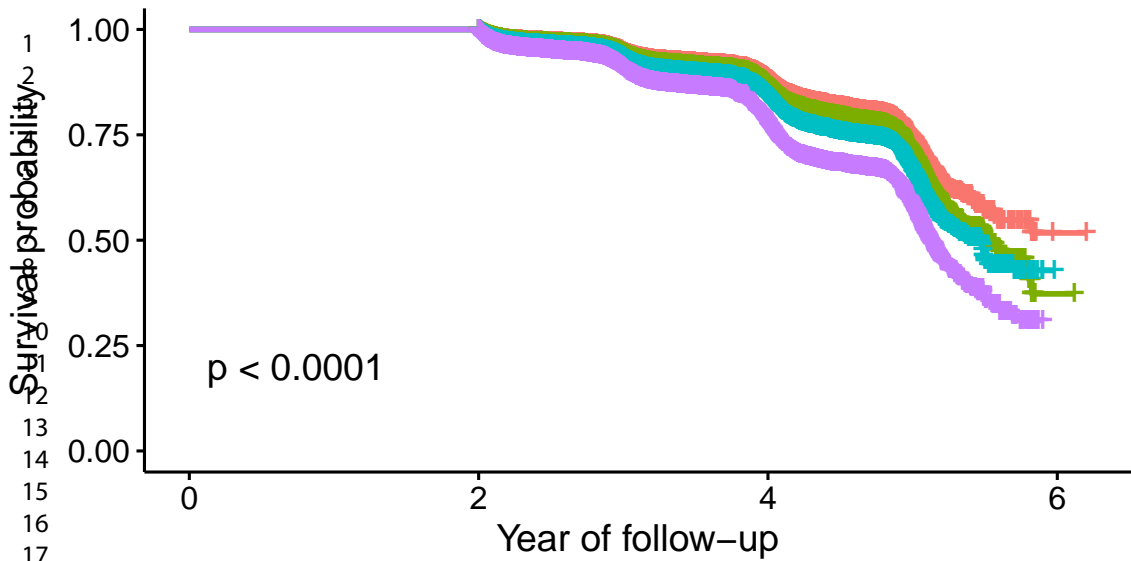
Characteristic	No of participants	HR (95%CI)	P value	P for interaction
Age, years				0.1335
<60	165813	1.008 (1.006, 1.009)	<0.0001	
≥60	16859	1.010 (1.007, 1.013)	<0.0001	
Gender				0.0002
Male	96966	1.006 (1.004, 1.008)	<0.0001	
Female	85706	1.011 (1.009, 1.013)	<0.0001	
BMI (kg/m ²)				<0.0001
<25	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.

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Number at risk

	2	3	4	5	6
PP	39914	21231	9935	2027	1
Q1	47771	24322	10844	2155	1
Q2	43811	21525	9281	1760	0
Q3	51176	24666	10207	2058	0

Year of follow-up

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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10-11
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

1	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
2			(b) Report category boundaries when continuous variables were categorized	12
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
4				
5	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
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11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	13-14
13	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
14	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
15	Generalisability	21	Discuss the generalisability (external validity) of the study results	16
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21	Other information			
22	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
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*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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1 **Nonlinear relationship between pulse pressure and the risk of**
2 **prediabetes: a secondary retrospective Chinese cohort study**

3 **Running title: PP and Pre-DM risk**

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4 45 **Abstract**

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6 46 **Objective:** Previous research has shown that pulse pressure has a significant role in the start and
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9 47 development of type 2 diabetes mellitus. However, there is little proof that pulse pressure and
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12 48 prediabetes are related. Our study aimed to investigate the relationship between pulse pressure and
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15 49 incident prediabetes in a substantial cohort of Chinese participants.

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17 50 **Design:** The 'DATADRYAD' database (www.Datadryad.org) was used to retrieve the data for this
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20 51 secondary retrospective cohort analysis.

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22 52 **Participants:** Data from 182672 Chinese individuals who participated in the medical examination
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25 53 program were recorded in this retrospective cohort study between 2010 and 2016 across 32 sites
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28 54 and 11 cities in China.

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30 55 **Setting:** Pulse pressure assessed at baseline and incident prediabetes during follow-up were the
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33 56 target-independent and dependent variables. The association between pulse pressure and
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36 57 prediabetes was investigated using Cox proportional hazards regression.

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38 58 **Primary outcome measures:** The outcome was incident prediabetes. Impaired fasting glucose
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41 59 levels (fasting blood glucose between 5.6 and 6.9 mmol/L) were used to define prediabetes.

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43 60 **Results:** After controlling for confounding variables, pulse pressure was positively correlated with
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46 61 incident prediabetes among Chinese adults (HR: 1.009, 95%CI: 1.007-1.010). Additionally, at a
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49 62 pulse pressure inflection point of 29 mmHg, a nonlinear connection between the pulse pressure
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52 63 and incident prediabetes was discovered. Increased pulse pressure was an independent risk factor
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55 64 for developing prediabetes when pulse pressure was greater than 29 mmHg. However, their
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58 65 association was not significant when pulse pressure was less than 29 mmHg. According to
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60 66 subgroup analyses, females, never smokers, and non-obesity correlated more significantly with

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4 67 pulse pressure and prediabetes.
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6 68 **Conclusion:** We discovered that higher pulse pressure independently correlated with prediabetes
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9 69 risk in this study of Chinese participants. The connection between pulse pressure and incident
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12 70 prediabetes was also nonlinear. High pulse pressure levels were related to a higher risk of
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15 71 prediabetes when pulse pressure was above 29 mmHg.
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4 89 **Article Summary**
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6 90 **Article focus**
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9 91 Our study investigated the relationship between PP and incident Pre-DM in a secondary
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11 92 retrospective cohort of Chinese participants.
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14 93 **Key Messages**
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17 94 We found that elevated PP was independently associated with an increased risk of Pre-DM in our
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19 95 study involving Chinese participants.
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22 96 Higher PP levels were associated with a greater risk of developing Pre-DM when PP exceeded 29
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24 97 mmHg.
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27 98 Further investigation is needed to understand PP's impact on the incident Pre-DM.
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30 99 **Strengths and limitations of this study**
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32 100 Our research leveraged a substantial sample size, drawing participants from multiple centers, thus
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34 101 ensuring a robust representation of the Chinese population.
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37 102 We elucidated a nonlinear relationship, marking the pioneering effort to pinpoint the inflection
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39 103 point of PP's impact on Pre-DM.
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42 104 Our subgroup analysis allowed us to delve into other potential risk factors within the PP and
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44 105 incident Pre-DM association.
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48 106 Our study did not incorporate a 2-hour oral glucose tolerance test or glycosylated hemoglobin
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50 107 level measurements, which could potentially lead to an underestimation of the incidence of
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52 108 Pre-DM.
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111 **Introduction**

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

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

133 **Methods**

134 **Data source**

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

140 **Study population**

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

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

154 **Data collection**

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4 155 Trained staff members gathered and compiled all of the data. Data from laboratory inspections
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7 156 were gathered in the original study under uniform conditions using standardized handling
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9 157 procedures. The skilled personnel, including height, blood pressure, body weight, and age,
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12 158 gathered demographic information. Professional trainees without light clothing and shoes measure
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14 159 individuals for weight and height. Weight/Height² (kg/m²) was used to compute BMI. Trained
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17 160 staff members took blood pressure using a standard mercury sphygmomanometer. A Beckman
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20 161 5800 autoanalyzer was used to measure laboratory data, such as low-density lipoprotein
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22 162 cholesterol (LDL-C), FPG, total cholesterol (TC), aspartate aminotransferase (AST), blood urea
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25 163 nitrogen (BUN), triglyceride (TG), alanine aminotransferase (ALT), serum creatinine (Scr), and
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27 164 high-density lipoprotein cholesterol (HDL-C). SBP (mmHg) - (DBP (mmHg)) were the formulas
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30 165 used to compute PP.

31 32 166 **Diagnosis of Pre-DM**

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35 167 Impaired fasting glucose levels (FPG between 5.6 and 6.9 mmol/L) were used to define
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38 168 Pre-DM[13].

39 40 169 **Patient and Public Involvement**

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43 170 Given this was a secondary retrospective cohort study, no patient was involved in the study.

44 45 171 **Statistical analysis**

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48 172 R software version 3.4.3 and EmpowerStats (R) version 4.0 were used for all statistical
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51 173 analyses.

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53 174 We initially assessed the baseline data distribution by categorizing it into quartiles based on the
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56 175 PP ($Q1 \leq 36$; $36 < Q2 \leq 43$; $43 < Q3 \leq 50$; $50 < Q4$). Continuous data were reported as medians with
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59 176 interquartile ranges (25th-75th percentile) or means with standard deviations (SD), while
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4 177 categorical data were expressed as frequencies and percentages. The Kruskal-Wallis H test,
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6 178 chi-square test, and one-way ANOVA were employed to assess disparities between PP groups.
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9 179 The cumulative incidence and terms person-year were used to represent incidence rates[14].
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11 180 Comparisons of survival and cumulative event rates were done using the Kaplan-Meier method.
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14 181 Using the log-rank test, we also examined the Kaplan-Meier hazard ratios (HR) of unfavorable
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17 182 events [15].

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19 183 There were 133257 (72.32%), 4240 (2.30%), 1541 (0.84%), 4209 (2.28%), 107684 (58.44%),
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22 184 82879 (44.98%), 18563 (10.07%), 83382 (45.25%), 9759 (5.30%) and 133257 (72.32%)
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25 185 individuals with missing data for smoking status, TG, ALT, TC, AST, LDL-C, BUN, HDL-C,
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27 186 SCr, and drinking status, respectively. The present study employed multiple imputations to handle
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30 187 the missing data of covariants. The imputation model included smoking status, BMI, TG, ALT,
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33 188 TC, AST, LDL-C, BUN, HDL-C, SCr, FPG, sex, family history of diabetes, drinking status, and
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35 189 age. Processes for missing data analysis employ the assumption of missing at random[16].

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38 190 This analysis assessed each factor's impact on incident Pre-DM using univariate Cox
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41 191 proportional hazards regression models. The multivariate Cox regression analysis also examined
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44 192 the precise connection between the PP and incident Pre-DM. In addition, we created three models
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47 193 (fully-adjusted, minimally-adjusted, and non-adjusted) to evaluate the connection between PP and
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49
50 194 incident Pre-DM. Suppose the HR is changed by at least 10% after the covariance is included in
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53 195 the model. At this point, the covariance should be adjusted[17].

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56 196 The current analysis conducted several sensitivity analyses to determine if the findings were
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58
59 197 trustworthy. We converted PP into a categorical variable based on the quartile. We computed the
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198 P for the trend to verify the outcomes of the PP as the continuous variable and test for

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4 199 nonlinearity. Obesity and older adults were connected to a greater occurrence of Pre-DM. Thus,
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6 200 we excluded individuals with BMI $\geq 25\text{kg/m}^2$ or age ≥ 60 years for subsequent sensitivity
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9 201 analyses to examine the connection between PP and Pre-DM risk. Additionally, we incorporated
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11 202 the continuous covariate as a curve to the equation using a generalized additive model (GAM) to
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13
14 203 confirm the validity of the results. We also calculated E-values to examine the possibility of
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16
17 204 unmeasured confounding between PP and the risk of prediabetes

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19 205 We used Cox proportional hazards regression with cubic spline functions and smooth curve
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21
22 206 fitting to explore the nonlinear relationship between PP and Pre-DM. We first utilized a recursive
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25 207 technique to locate the inflection point if a non-linear relationship was discovered[18]. The
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28 208 recursive algorithm commences with an arbitrary initialization and subsequently undergoes a
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31 209 series of filtering and smoothing steps in order to identify the inflection point accurately.
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33 210 Following this, we construct a two-piece Cox proportional hazards regression model, separately
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35
36 211 analyzing the data on either side of the inflection point. Ultimately, the study determined the most
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38 212 appropriate model for PP's connection with Pre-DM through log-likelihood ratio analysis.

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40 213 Subgroup analysis, utilizing the Cox proportional hazard model, was also conducted. Firstly,
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43 214 these variables were selected based on a combination of clinical relevance, literature review, and
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45
46 215 the availability of data within our cohort. Secondly, the interaction test between these variables
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49 216 and PP was performed before the subgroup analysis. The likelihood ratio test was used to compare
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52 217 models with and without the multiplicative interaction term. Secondly, stratification was
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55 218 performed based on medians or established clinical cut points[19], and variables such as age (<60 ,
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57 219 ≥ 60 years) and BMI (<25 , ≥ 25 kg/m²) were converted into categorical factors. Thirdly, a fully
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59 220 adjusted analysis was performed for each stratum, except for the stratification factor. Ultimately,
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4 221 the likelihood ratio test was used to determine whether interaction terms existed in models with
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6 222 and without interaction terms[20, 21]. The study adhered to the STROBE statement for all
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9 223 outcomes[17, 22]. Statistical significance was determined by a P-value < 0.05, using two-tailed
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12 224 tests.

14 225 **Results**

16 226 **Characteristics of individuals**

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18
19 227 In the current research, 182672 individuals deemed free of Pre-DM at baseline were included.
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21
22 228 The average age was 40.832 ± 11.864 years, and 53.082% of individuals were male. Twenty
23
24 229 thousand two hundred eighty-four individuals eventually got Pre-DM after an average of 3.143
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26
27 230 years of follow-up. Table 1 displays comprehensive clinical measurements, biochemical tests, and
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29
30 231 various parameters. We categorized participants into subgroups based on PP quartiles ($Q1 \leq 36$;
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32 232 $36 < Q2 \leq 43$; $43 < Q3 \leq 50$; $50 < Q4$). Compared to the Q1 group, the other groups (Q2 group, Q3
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35 233 group, Q4 group) had higher ALT, BMI, age, TG, Scr, TC, AST, BUN, LDL-C, and lower
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38 234 HDL-C. Additionally, the Q4 group had a higher proportion of men, smokers, and drinkers.

39 235 **The incidence rate of Pre-DM**

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42 236 During the follow-up, 20284 individuals developed incident Pre-DM, as outlined in
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45 237 Supplemental Table 1. All people had a prevalence rate of 11.10%. The four PP groups'
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48 238 prevalence rates were 8.92%, 9.47% (9.21%–9.73%), 10.82%, and 14.58%. In addition, the
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50
51 239 cumulative incidence rate of the overall population and four PP groups were 3532.68, 2779.24,
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53 240 2999.95, 3470.06, and 4701.37 per 100,000 person-years, respectively. Individuals in the Q2, Q3,
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56 241 and Q4 groups exhibited significantly greater cumulative incidence and prevalence rates of
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59 242 Pre-DM than those in the Q1 group.
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4 243 The Kaplan-Meier curves for the propensity to survive without Pre-DM are shown in
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6 244 Supplemental Figure 1. There was a significant difference between the four PP groups regarding
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9 245 the likelihood of developing Pre-DM ($P<0.0001$). As PP levels increased, the chance of living
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11 246 without prediabetes steadily dropped. As a result, Pre-DM risk was highest among those in the
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13
14 247 highest PP categories.

17 248 **Univariate analysis**

19 249 Supplemental Table 2 presents the findings of the univariate analysis. DBP, TC, BMI, SBP,
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21
22 250 FPG, age, TG, SCr, LDL-C, PP, and BUN were correlated with Pre-DM risk. HDL-C exhibits an
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24
25 251 inverse relationship with Pre-DM risk. Individuals who never drink or smoke also have a lower
26
27 252 risk of developing pre-DM. Pre-DM risk was shown to be greater in men than in women.

30 253 **The results of the connection between PP and Pre-DM**

32 254 The Cox proportional hazard regression models for the association between PP and Pre-DM are
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34
35 255 shown in Table 2. In the non-adjusted model, the HR (95%CI) for the relationship between
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38 256 Pre-DM and PP was 1.025 (1.023-1.026). The HR (95%CI) in the minimally-adjusted model was
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41 257 1.013 (1.011-1.014) after adjusting for smoking status, age, BMI, family history of diabetes,
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43 258 gender, and drinking status. The HR (95%CI) was 1.009 (1.007-1.010) in the fully-adjusted model
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46 259 after controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex,
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48 260 FPG, family history of diabetes, drinking status, and age. The findings showed that for every
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50
51 261 1mmHg rise in PP, the risk of Pre-DM rose by 0.9%.

53 262 **Sensitivity analyses**

56 263 We used several sensitivity analyses to evaluate how reliable our results were. PP was changed
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58 264 from a continuous to a categorical variable before being reintroduced into the model. Following
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4 265 the translation of PP into categorical variables, the trend p was not equal, suggesting a potential
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6 266 nonlinear connection between PP and the chance of developing Pre-DM. Additionally, a GAM
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9 267 added the continuity covariate to the equation. Results for the GAM model showed a positive
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12 268 connection between PP and the probability of developing Pre-DM (HR: 1.008,
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14 269 95%CI:1.007-1.010) (Table 2).

17 270 Besides, the current research excluded participants with BMI<25kg/m² for sensitivity analysis.
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19 271 After controlling for confounding factors, we observed a positive association between PP and
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22 272 Pre-DM risk (HR: 1.011, 95%CI: 1.009-1.013) (Supplemental Table 3). Moreover, we considered
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24 273 participants with ages < 60 years for sensitivity studies. After adjusting for smoking status, BMI,
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27 274 TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking
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29
30 275 status, and age, the results showed that PP remained positively correlated with the likelihood of
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33 276 developing Pre-DM (HR: 1.008, 95%CI: 1.007-1.010). (Supplemental Table 3). According to the
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35 277 sensitivity analysis, our findings appeared to be solid.

37 278 Additionally, an E-value was computed to assess the vulnerability of the study results to
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39 279 potential unobserved confounding factors. The resulting E-value (1.21) demonstrated a higher
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42 280 level of statistical significance in comparison to the relative risk (1.05) associated with
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44 281 unmeasured confounders and PP. This suggests that the impact of unmeasured or unidentified
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47 282 confounders on the relationship between PP and the occurrence of Pre-DM was negligible.

283 **The analysis of the nonlinear connection**

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53 284 The nonlinear connection between PP and incident Pre-DM is illustrated in Figure 2. After
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56 285 correcting for confounding factors, there was a nonlinear link between PP and incident Pre-DM
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59 286 (Table 3). Based on a two-piecewise Cox proportional hazards regression model, the PP's
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4 287 inflection point was 29 mmHg (P for log-likelihood ratio test = 0.008). When PP was more than
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7 288 29 mmHg, PP was strongly linked with incident Pre-DM (HR:1.009, 95%CI: 1.008-1.011,
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9 289 P<0.0001). However, their correlation was not significant when PP was less than 29 mmHg (HR:
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11 290 0.990, 95%CI: 0.977-1.003, P=0.1492).

14 291 **The results of the subgroup analysis**

17 292 Interaction tests performed before subgroup analyses showed that age, BMI, gender, family
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19 293 history of diabetes, smoking status, and drinking status interacted with PP (P<0.001)
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21
22 294 (Supplemental Table 4). We selected age, BMI, gender, family history of diabetes, smoking status,
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25 295 and drinking status as stratification variables and examined the changes in their impact sizes
26
27 296 (Supplemental Table 5). Age, drinking status, and family history of diabetes had no impact on the
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30 297 correlation between PP and the risk of prediabetes. Females, never smokers, ever smokers, and
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32 298 subjects with BMI<25 kg/m² were more likely to be associated with prediabetes risk. Conversely,
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35 299 there was a weaker connection in males, current smokers, and individuals with BMI≥25 kg/m².

37 300 **Discussion**

40 301 The current study's main goal was to investigate the connection between PP and incident
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42 302 Pre-DM in Chinese participants. The findings demonstrated a correlation between increased PP
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45 303 and a higher risk of prediabetes. The correlation between PP and Pre-DM was also investigated on
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48 304 the left and right sides of the inflection point. PP level and incident prediabetes have a nonlinear
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51 305 relationship. It was found that never-smokers, ever-smokers, females, and individuals with
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53 306 BMI<25 kg/m² had a greater correlation between PP and incident Pre-DM.

56 307 PP, the arithmetic difference between SBP and DBP, is determined by arterial wall elasticity
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58 308 and is related to all-cause mortality, cardiovascular events, stroke, kidney injury, severe eye
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4 309 illness, and arterial stiffness[23-28]. In comparison to blood pressure, PP has a better predictive
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6 310 capacity for poor cardiovascular outcomes in people with diabetes, according to several previous
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9 311 pieces of evidence[6, 29]. In addition, some studies found that PP demonstrated strong predictive
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11 312 ability in the homeostatic model assessment of insulin resistance index, diabetes, and metabolic
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14 313 syndrome[30-32]. In a retrospective study involving 211814 Chinese participants, after controlling
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17 314 for BMI, smoking and drinking status, age, TC, gender, family history of diabetes, FPG, TG, and
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20 315 BUN and ALT, Higher PP levels independently connect with increased T2DM risk (HR:1.003,
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22 316 95%CI:1.001,1.005)[11]. In a longitudinal study involving 12272 Chinese, Zhang L et al.[30]
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25 317 found that high PP in Chinese women may be related to the development of T2DM after adjusting
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28 318 for confounding covariates. In a national cross-sectional study involving 6187 Korean older
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31 319 adults, Kwon YJ et al.[32] discovered a positive association between PP and metabolic syndrome
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33 320 after adjusting for alcohol consumption, smoking, age, regular exercise, and mean arterial blood
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36 321 pressure. In another cross-sectional cohort study that included 38708 rural Chinese participants,
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39 322 compared with the lowest group, the odds ratio (95%CI) of PP in the highest quartile of risk for
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42 323 metabolic syndrome was found to be 1.81 (1.67-1.95) after controlling for confounders[33]. In
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45 324 addition, in a prospective research enrolling 32917 Chinese, the HR (95%CI) for diabetes in the
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48 325 Q3 and Q4 groups were 1.13 (1.04-1.22) and 1.14 (1.05-1.24), respectively, after adjusting for
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51 326 covariates compared to the Q1 group[34]. However, in a multicenter, longitudinal cohort study
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54 327 that included 18619 adults, high PP was not related to an increased risk of diabetes after adjusting
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57 328 for BMI, mean arterial pressure, gender, high-sensitivity C reactive protein, age, exercise,
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60 329 smoking, blood pressure lowering agents, drinking, hyperlipidemia, and family history of
330 diabetes[35]. A retrospective study of 178 individuals with hypertension found that PP was not

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4 331 associated with the risk of new-onset diabetes after adjusting for potential confounders[36]. This
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6 332 retrospective cohort study involved 182672 Chinese individuals and revealed a higher incidence of
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9 333 prediabetes at increased PP levels. After adjusting for smoking status, BMI, TG, ALT, TC, AST,
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11 334 LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the
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14 335 results indicated that each unit of the LAP raised the risk of prediabetes by 0.9%. Moreover,
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17 336 sensitivity analysis has demonstrated that this correlation remains observable in Chinese adults
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19 337 with age <60 years or BMI <25 kg/m². The efforts mentioned above have demonstrated the
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22 338 consistency of the connection between PP and Pre-DM risk. The findings offered a clinical
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25 339 PP-level intervention guideline to decrease Pre-DM risk.

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27 340 Few previous studies have investigated the probable curvilinear link between PP and
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30 341 prediabetes. The current study first examined the nonlinear association between PP and
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33 342 prediabetes. After controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN,
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36 343 HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the findings revealed
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38 344 that the connection between PP and prediabetes was nonlinear. Based on a two-piecewise Cox
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41 345 proportional hazards regression model, we identified the inflection point of PP as 29 mmHg.
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43 346 When PP levels exceeded 29 mmHg, a 1-unit increase in PP correlated with a 0.9% increase in the
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45
46 347 hazard ratio (HR) for individuals with Pre-DM (HR: 1.009, 95% CI: 1.008-1.011, P<0.0001).
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48 348 However, no significant correlation was observed between PP levels below 29 mmHg and the
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51 349 incident Pre-DM (HR: 0.990, 95% CI: 0.977-1.003, P = 0.1492). Elevated PP serves as a valuable
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54 350 indicator for identifying high-risk participants likely to develop Pre-DM during follow-up.
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56 351 Moreover, our analysis revealed that the relationship between PP and the emergence of Pre-DM
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59 352 was more pronounced in never-smokers, ever-smokers, females, and individuals with BMI< 25
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4 353 kg/m². In contrast, this association appeared attenuated in males, current smokers, and individuals
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7 354 with BMI \geq 25 kg/m². Prior research has consistently identified obesity, smoking, and male as
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9 355 contributors to insulin resistance[37, 38], which is a precursor to Pre-DM. We postulated that the
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11 356 attenuated association observed in these subgroups may be attributable to the overriding influence
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14 357 of these risk factors on the pathogenesis of Pre-DM. The direct impact of PP on prediabetes risk
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17 358 may be somewhat eclipsed by the more substantial effects of obesity, active smoking, and the
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19 359 male sex on insulin resistance and subsequent Pre-DM development. This information can remind
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22 360 individuals to adopt healthier lifestyle habits sooner, ultimately improving their outcomes.
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25 361 The mechanism behind the association between PP and prediabetes is yet unknown. Several
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27 362 explanations currently exist for PP leading to Pre-DM. Firstly, endothelial cell dysfunction may
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30 363 result in microvascular dysfunction[39], which in turn causes dysfunctional glucose metabolism,
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33 364 insulin resistance, poor tissue perfusion, and arterial stiffness[40-42]. Additionally, arterial
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35 365 stiffness may exacerbate microvascular lesions, creating a vicious cycle[43, 44]. Secondly, normal
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38 366 arteries can reduce PP, but arterial stiffness increases blood flow through low-resistance organs
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41 367 (such as the kidney and brain), which will cause organ dysfunction[45]. As a low-resistance,
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43 368 high-blood-flow organ with a mean tissue perfusion of 250–300 ml/min/100g, the pancreas may
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45 369 be negatively impacted by arterial stiffness in terms of its endocrine function.
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48 370 The current research possesses several notable advantages. Firstly, we delved deeper into the
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51 371 nonlinear relationship between PP and prediabetes. Secondly, we minimized the impact of residual
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53 372 confounding factors through rigorous statistical adjustments. Thirdly, we conducted sensitivity
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56 373 analyses to ensure the robustness of our findings. Lastly, we performed a group analysis to
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59 374 evaluate other potential risk covariates that could affect the link between PP and Pre-DM.
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4 375 The present study has certain limitations. First, this study is based on a Chinese population, and
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6 376 while it offers valuable insights, the findings might not be directly generalizable to other
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9 377 populations due to genetic, lifestyle, and environmental differences. In the future, we will explore
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11 378 the relationship between PP and prediabetes risk in diverse populations. Second, as our study was
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14 379 a secondary analysis, we cannot guarantee data quality monitoring and variable control. In
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17 380 forthcoming research endeavors, we will endeavor to construct prospective cohort studies with
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19 381 enhanced data quality oversight and variable control, thereby mitigating bias. Third, the original
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22 382 study excluded people with diabetes at baseline or those with missing data, which may have
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25 383 affected the representativeness of the sample. In the future, we will design our own study in a
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27 384 more diverse population to validate our findings. Fourth, prediabetes was defined based on
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29 385 impaired fasting glucose levels in our study. This could potentially lead to underestimation of
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32 386 prediabetes incidence. This is a secondary retrospective study, and the raw data did not provide
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35 387 information regarding 2-hour oral glucose tolerance test or glycosylated hemoglobin level
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38 388 measurements. In the future, we will consider designing our study to document more variables,
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40 389 including 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements.
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43 390 Fifth, as with all observational studies, there may be uncontrolled or unmeasured confounding
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45 391 factors, such as diet, exercise, atherosclerosis, the use of antihypertensive medications, and the
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48 392 presence of hypertension, despite controlling for known potential confounders like BMI, TC,
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51 393 LDL-C, AST, ALT, Scr, BUN, and FPG. However, we used the E-value to evaluate the impact of
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53 394 unmeasured confounders and determined it unlikely that they fully explained the results. Sixth,
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56 395 SBP and DBP were only measured at baseline in the original study, and we did not assess how
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58 396 SBP and DBP changed over time. In the future, we will consider designing our own study and
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4 397 documenting more information, such as diet, exercise, atherosclerosis, antihypertensive
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6 398 medications, the presence of hypertension and changes in blood pressure over time, and then
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9 399 utilizing a GAM model to explore the impact of changes in PP on Pre-DM risk.
10

11 400 **Conclusion**

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14 401 This cohort study of the Chinese population shows that PP was inversely and non-linearly
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16 402 associated with the incidence of Pre-DM after adjusting for other confounding factors. High PP
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18 403 levels were related to Pre-DM risk when PP was above 29 mmHg. From a therapeutic standpoint,
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20 404 lowering the PP below the inflection point represents a cost-effective and straightforward
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22 405 approach for the early prevention and intervention of Pre-DM.
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30 407 **Declarations**

31 408 **Ethics approval and consent to participate**

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34 409 The original study followed guidelines outlined by the Helsinki Declaration and was approved by
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36 410 the Rich Healthcare Group Review Board. In addition, the Rich Healthcare Group Review Board
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38 411 has waived informed consent for the current retrospective study. All methods were performed in
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40 412 accordance with the relevant the Declaration of Helsinki.
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45 413 **Consent for publication**

46
47 414 Not applicable.
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50 415 **Availability of data and materials**

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52 416 The authors confirm that the data supporting the findings of this study are available within the
53
54 417 article [and/or its supplementary materials].
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58 418 **Competing interests**

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4 419 The authors declare that they have no competing interests.
5

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19 425 **Author contributions**
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22 426 Changchun Cao and Yong Han contributed to the study concept and design, researched and
23
24 427 interpreted the data, and drafted the manuscript. Haofei Hu, Yongcheng He, and Jiao Luo
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26 428 analyzed the data and reviewed the manuscript. Changchun Cao and Yong Han oversaw the
27
28 429 project's progress, contributed to the discussion, and reviewed the manuscript. Haofei Hu,
29
30 430 Yongcheng He, and Jiao Luo were the guarantors of this work. As such, they had full access to all
31
32 431 data in the study and were responsible for the data integrity and analysis accuracy. All authors
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34 432 read and approved the final manuscript.
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40 433 **Acknowledgments**
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42 434 Not applicable.
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441 **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

442 Values are n (%) or mean ± SD

443 PP: pulse pressure, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, ALT

444 alanine aminotransferase, AST aspartate aminotransferase, HDL-C high-density lipoprotein cholesterol, LDL-C

445 low-density lipoprotein cholesterol, TC total cholesterol, TG triglycerides, Scr serum creatinine, BUN blood urea

446 nitrogen, FPG fasting plasma glucose

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454 **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)	1.009 (1.007, 1.010)	1.008 (1.007, 1.010) <0.00001
PP		<0.00001	<0.00001	
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-smoke		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

455 Crude model: we did not adjust for other covariants.

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

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

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

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

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484 **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	

485 We adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG, HDL-C, LDL-C, AST,

486 ALT, SCr, BUN, and FPG.

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

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4 515 **Figure 1** Study Population
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6 516 **Figure 2** The nonlinear relationship between PP and incident prediabetes. A nonlinear
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9 517 relationship between PP and incident prediabetes was detected after adjusting for
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12 518 smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG,
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14 519 family history of diabetes, drinking status, and age.
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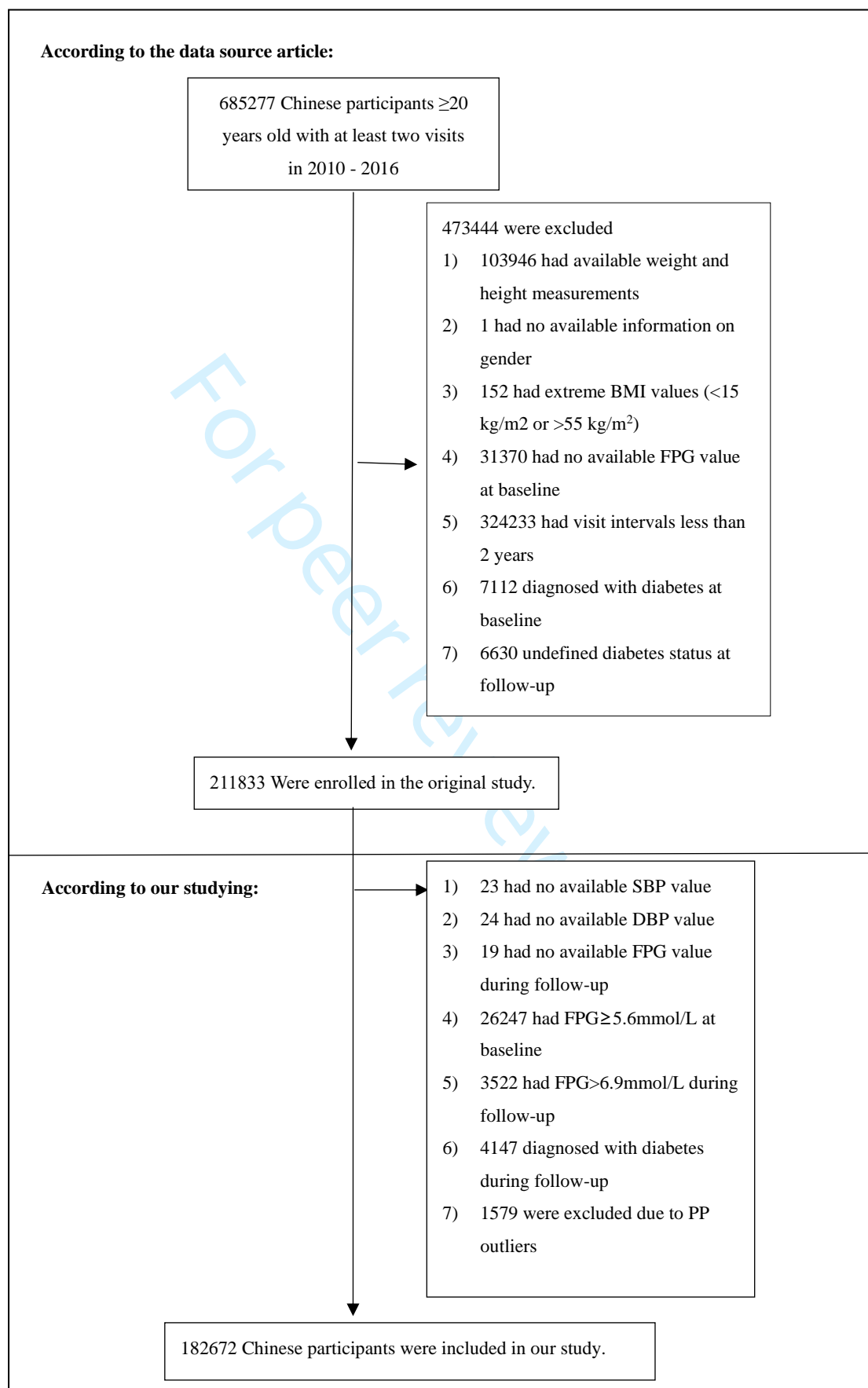
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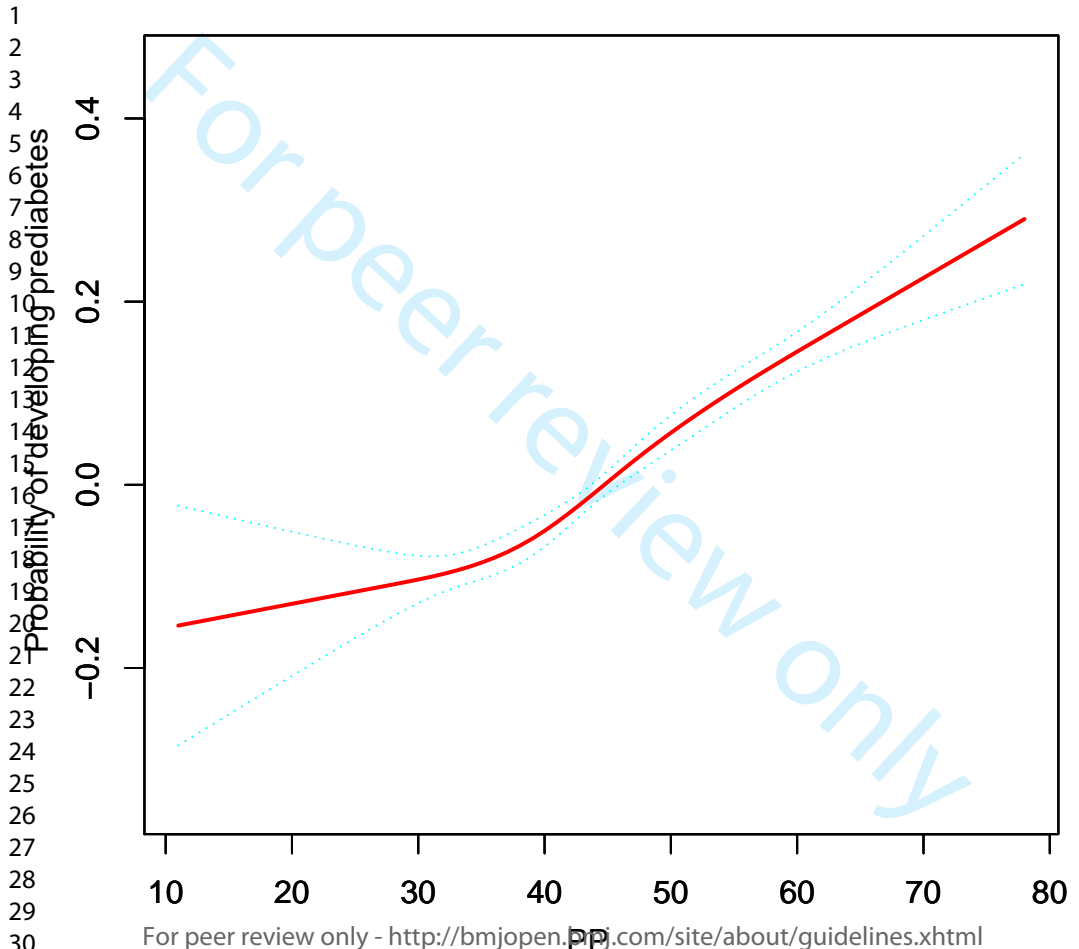
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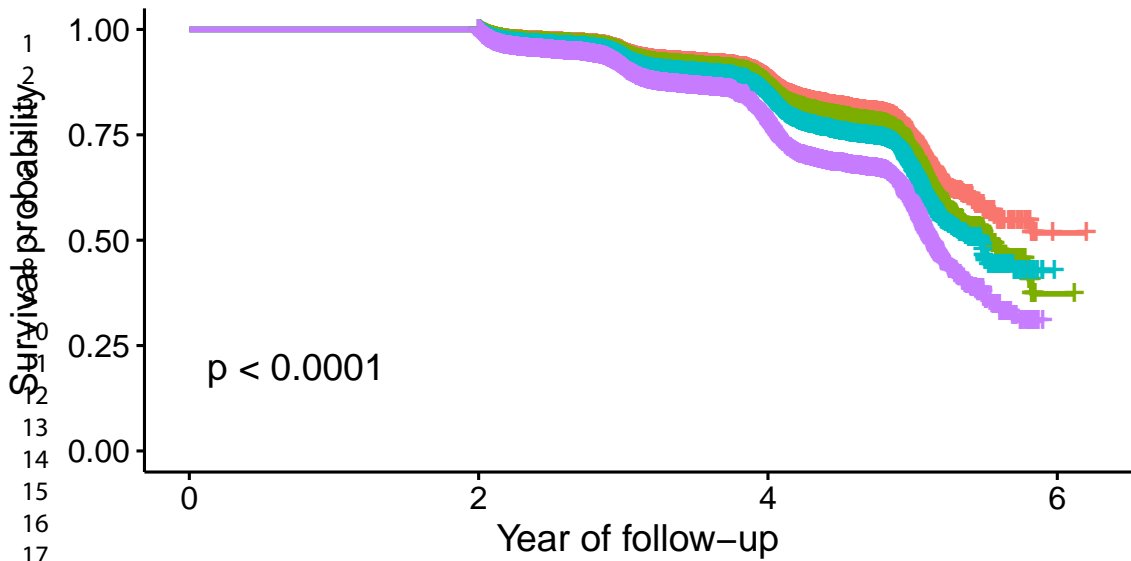
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Number at risk

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PP	39914	21231	9935	2027	1
Q1	47771	24322	10844	2155	1
Q2	43811	21525	9281	1760	0
Q3	51176	24666	10207	2058	0

Year of follow-up

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/m ²)	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 \geq 25kg/m². 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 \geq 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

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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
FBG (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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10-11
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

1	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
2			(b) Report category boundaries when continuous variables were categorized	12
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
4				
5	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
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11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	13-14
13	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
14	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
15	Generalisability	21	Discuss the generalisability (external validity) of the study results	16
16				
17	Other information			
18	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
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*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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1 **Nonlinear relationship between pulse pressure and the risk of**
2 **prediabetes: a secondary retrospective Chinese cohort study**

3 **Running title: PP and Pre-DM risk**

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45 Abstract

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

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

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

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

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

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

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4 67 pulse pressure and prediabetes.
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6 68 **Conclusion:** We discovered that higher pulse pressure independently correlated with prediabetes
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9 69 risk in this study of Chinese participants. The connection between pulse pressure and incident
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12 70 prediabetes was also nonlinear. High pulse pressure levels were related to a higher risk of
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15 71 prediabetes when pulse pressure was above 29 mmHg.
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For peer review only

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4 89 **Article Summary**
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6 90 **Article focus**
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9 91 Our study investigated the relationship between PP and incident Pre-DM in a secondary
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12 92 retrospective cohort of Chinese participants.
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14 93 **Strengths and limitations of this study**
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17 94 ● Our research leveraged a substantial sample size, drawing participants from multiple
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19 95 centers, thus ensuring a robust representation of the Chinese population.
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22 96 ● We elucidated a nonlinear relationship, marking the pioneering effort to pinpoint the
23
24 97 inflection point of PP's impact on Pre-DM.
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27 98 ● Our subgroup analysis allowed us to delve into other potential risk factors within the PP
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29 99 and incident Pre-DM association.
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32 100 ● Our study did not incorporate a 2-hour oral glucose tolerance test or glycosylated
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34 101 hemoglobin level measurements, which could potentially lead to an underestimation of the
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36 102 incidence of Pre-DM.
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111 **Introduction**

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

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

133 **Methods**

134 **Data source**

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

140 **Study population**

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

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

154 **Data collection**

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4 155 Trained staff members gathered and compiled all of the data. Data from laboratory inspections
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6 156 were gathered in the original study under uniform conditions using standardized handling
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9 157 procedures. The skilled personnel, including height, blood pressure, body weight, and age,
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12 158 gathered demographic information. Professional trainees without light clothing and shoes measure
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14 159 individuals for weight and height. Weight/Height² (kg/m²) was used to compute BMI. Trained
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17 160 staff members took blood pressure using a standard mercury sphygmomanometer. A Beckman
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19 161 5800 autoanalyzer was used to measure laboratory data, such as low-density lipoprotein
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22 162 cholesterol (LDL-C), FPG, total cholesterol (TC), aspartate aminotransferase (AST), blood urea
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25 163 nitrogen (BUN), triglyceride (TG), alanine aminotransferase (ALT), serum creatinine (Scr), and
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27 164 high-density lipoprotein cholesterol (HDL-C). SBP (mmHg) - (DBP (mmHg)) were the formulas
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30 165 used to compute PP.

32 166 **Diagnosis of Pre-DM**

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35 167 Impaired fasting glucose levels (FPG between 5.6 and 6.9 mmol/L) were used to define
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38 168 Pre-DM[13].

40 169 **Patient and Public Involvement**

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43 170 Given this was a secondary retrospective cohort study, no patient was involved in the study.

45 171 **Statistical analysis**

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48 172 R software version 3.4.3 and EmpowerStats (R) version 4.0 were used for all statistical
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51 173 analyses.

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53 174 We initially assessed the baseline data distribution by categorizing it into quartiles based on the
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56 175 PP ($Q1 \leq 36$; $36 < Q2 \leq 43$; $43 < Q3 \leq 50$; $50 < Q4$). Continuous data were reported as medians with
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59 176 interquartile ranges (25th-75th percentile) or means with standard deviations (SD), while
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4 177 categorical data were expressed as frequencies and percentages. The Kruskal-Wallis H test,
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6 178 chi-square test, and one-way ANOVA were employed to assess disparities between PP groups.
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9 179 The cumulative incidence and terms person-year were used to represent incidence rates[14].
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11 180 Comparisons of survival and cumulative event rates were done using the Kaplan-Meier method.
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14 181 Using the log-rank test, we also examined the Kaplan-Meier hazard ratios (HR) of unfavorable
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17 182 events [15].

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19 183 There were 133257 (72.32%), 4240 (2.30%), 1541 (0.84%), 4209 (2.28%), 107684 (58.44%),
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22 184 82879 (44.98%), 18563 (10.07%), 83382 (45.25%), 9759 (5.30%) and 133257 (72.32%)
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25 185 individuals with missing data for smoking status, TG, ALT, TC, AST, LDL-C, BUN, HDL-C,
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27 186 SCr, and drinking status, respectively. The present study employed multiple imputations to handle
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30 187 the missing data of covariants. The imputation model included smoking status, BMI, TG, ALT,
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33 188 TC, AST, LDL-C, BUN, HDL-C, SCr, FPG, sex, family history of diabetes, drinking status, and
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35 189 age. Processes for missing data analysis employ the assumption of missing at random[16].

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38 190 This analysis assessed each factor's impact on incident Pre-DM using univariate Cox
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41 191 proportional hazards regression models. The multivariate Cox regression analysis also examined
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44 192 the precise connection between the PP and incident Pre-DM. In addition, we created three models
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47 193 (fully-adjusted, minimally-adjusted, and non-adjusted) to evaluate the connection between PP and
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50 194 incident Pre-DM. Suppose the HR is changed by at least 10% after the covariance is included in
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53 195 the model. At this point, the covariance should be adjusted[17].

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56 196 The current analysis conducted several sensitivity analyses to determine if the findings were
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59 197 trustworthy. We converted PP into a categorical variable based on the quartile. We computed the
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198 P for the trend to verify the outcomes of the PP as the continuous variable and test for

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4 199 nonlinearity. Obesity and older adults were connected to a greater occurrence of Pre-DM. Thus,
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6 200 we excluded individuals with BMI $\geq 25\text{kg/m}^2$ or age ≥ 60 years for subsequent sensitivity
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9 201 analyses to examine the connection between PP and Pre-DM risk. Additionally, we incorporated
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11 202 the continuous covariate as a curve to the equation using a generalized additive model (GAM) to
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14 203 confirm the validity of the results. We also calculated E-values to examine the possibility of
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17 204 unmeasured confounding between PP and the risk of prediabetes

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19 205 We used Cox proportional hazards regression with cubic spline functions and smooth curve
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22 206 fitting to explore the nonlinear relationship between PP and Pre-DM. We first utilized a recursive
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25 207 technique to locate the inflection point if a non-linear relationship was discovered[18]. The
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28 208 recursive algorithm commences with an arbitrary initialization and subsequently undergoes a
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31 209 series of filtering and smoothing steps in order to identify the inflection point accurately.
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34 210 Following this, we construct a two-piece Cox proportional hazards regression model, separately
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37 211 analyzing the data on either side of the inflection point. Ultimately, the study determined the most
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40 212 appropriate model for PP's connection with Pre-DM through log-likelihood ratio analysis.

41 213 Subgroup analysis, utilizing the Cox proportional hazard model, was also conducted. Firstly,
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43 214 these variables were selected based on a combination of clinical relevance, literature review, and
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46 215 the availability of data within our cohort. Secondly, the interaction test between these variables
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49 216 and PP was performed before the subgroup analysis. The likelihood ratio test was used to compare
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52 217 models with and without the multiplicative interaction term. Secondly, stratification was
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55 218 performed based on medians or established clinical cut points[19], and variables such as age (<60 ,
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58 219 ≥ 60 years) and BMI (<25 , ≥ 25 kg/m²) were converted into categorical factors. Thirdly, a fully
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60 220 adjusted analysis was performed for each stratum, except for the stratification factor. Ultimately,

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4 221 the likelihood ratio test was used to determine whether interaction terms existed in models with
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6 222 and without interaction terms[20, 21]. The study adhered to the STROBE statement for all
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9 223 outcomes[17, 22]. Statistical significance was determined by a P-value < 0.05, using two-tailed
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12 224 tests.

14 225 **Results**

17 226 **Characteristics of individuals**

19 227 In the current research, 182672 individuals deemed free of Pre-DM at baseline were included.
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22 228 The average age was 40.832 ± 11.864 years, and 53.082% of individuals were male. Twenty
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24 229 thousand two hundred eighty-four individuals eventually got Pre-DM after an average of 3.143
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27 230 years of follow-up. Table 1 displays comprehensive clinical measurements, biochemical tests, and
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30 231 various parameters. We categorized participants into subgroups based on PP quartiles ($Q1 \leq 36$;
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32 232 $36 < Q2 \leq 43$; $43 < Q3 \leq 50$; $50 < Q4$). Compared to the Q1 group, the other groups (Q2 group, Q3
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35 233 group, Q4 group) had higher ALT, BMI, age, TG, Scr, TC, AST, BUN, LDL-C, and lower
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38 234 HDL-C. Additionally, the Q4 group had a higher proportion of men, smokers, and drinkers.

40 235 **The incidence rate of Pre-DM**

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43 236 During the follow-up, 20284 individuals developed incident Pre-DM, as outlined in
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45
46 237 Supplemental Table 1. All people had a prevalence rate of 11.10%. The four PP groups'
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48 238 prevalence rates were 8.92%, 9.47% (9.21%–9.73%), 10.82%, and 14.58%. In addition, the
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51 239 cumulative incidence rate of the overall population and four PP groups were 3532.68, 2779.24,
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53 240 2999.95, 3470.06, and 4701.37 per 100,000 person-years, respectively. Individuals in the Q2, Q3,
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56 241 and Q4 groups exhibited significantly greater cumulative incidence and prevalence rates of
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59 242 Pre-DM than those in the Q1 group.
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4 243 The Kaplan-Meier curves for the propensity to survive without Pre-DM are shown in
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6 244 Supplemental Figure 1. There was a significant difference between the four PP groups regarding
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9 245 the likelihood of developing Pre-DM ($P<0.001$). As PP levels increased, the chance of living
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11 246 without prediabetes steadily dropped. As a result, Pre-DM risk was highest among those in the
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14 247 highest PP categories.

248 **Univariate analysis**

19 249 Supplemental Table 2 presents the findings of the univariate analysis. DBP, TC, BMI, SBP,
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22 250 FPG, age, TG, SCr, LDL-C, PP, and BUN were correlated with Pre-DM risk. HDL-C exhibits an
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25 251 inverse relationship with Pre-DM risk. Individuals who never drink or smoke also have a lower
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27 252 risk of developing pre-DM. Pre-DM risk was shown to be greater in men than in women.

253 **The results of the connection between PP and Pre-DM**

32 254 The Cox proportional hazard regression models for the association between PP and Pre-DM are
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35 255 shown in Table 2. In the non-adjusted model, the HR (95%CI) for the relationship between
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38 256 Pre-DM and PP was 1.025 (1.023-1.026). The HR (95%CI) in the minimally-adjusted model was
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41 257 1.013 (1.011-1.014) after adjusting for smoking status, age, BMI, family history of diabetes,
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43 258 gender, and drinking status. The HR (95%CI) was 1.009 (1.007-1.010) in the fully-adjusted model
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45
46 259 after controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex,
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48 260 FPG, family history of diabetes, drinking status, and age. The findings showed that for every
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51 261 1mmHg rise in PP, the risk of Pre-DM rose by 0.9%.

262 **Sensitivity analyses**

56 263 We used several sensitivity analyses to evaluate how reliable our results were. PP was changed
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59 264 from a continuous to a categorical variable before being reintroduced into the model. Following
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4 265 the translation of PP into categorical variables, the trend p was not equal, suggesting a potential
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6 266 nonlinear connection between PP and the chance of developing Pre-DM. Additionally, a GAM
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9 267 added the continuity covariate to the equation. Results for the GAM model showed a positive
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12 268 connection between PP and the probability of developing Pre-DM (HR: 1.008,
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14 269 95%CI:1.007-1.010) (Table 2).

17 270 Besides, the current research excluded participants with BMI<25kg/m² for sensitivity analysis.
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19 271 After controlling for confounding factors, we observed a positive association between PP and
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22 272 Pre-DM risk (HR: 1.011, 95%CI: 1.009-1.013) (Supplemental Table 3). Moreover, we considered
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24 273 participants with ages < 60 years for sensitivity studies. After adjusting for smoking status, BMI,
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27 274 TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking
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30 275 status, and age, the results showed that PP remained positively correlated with the likelihood of
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33 276 developing Pre-DM (HR: 1.008, 95%CI: 1.007-1.010). (Supplemental Table 3). According to the
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35 277 sensitivity analysis, our findings appeared to be solid.

37 278 Additionally, an E-value was computed to assess the vulnerability of the study results to
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39 279 potential unobserved confounding factors. The resulting E-value (1.21) demonstrated a higher
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42 280 level of statistical significance in comparison to the relative risk (1.05) associated with
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44 281 unmeasured confounders and PP. This suggests that the impact of unmeasured or unidentified
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47 282 confounders on the relationship between PP and the occurrence of Pre-DM was negligible.

283 **The analysis of the nonlinear connection**

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53 284 The nonlinear connection between PP and incident Pre-DM is illustrated in Figure 2. After
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56 285 correcting for confounding factors, there was a nonlinear link between PP and incident Pre-DM
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59 286 (Table 3). Based on a two-piecewise Cox proportional hazards regression model, the PP's
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4 287 inflection point was 29 mmHg (P for log-likelihood ratio test = 0.008). When PP was more than
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7 288 29 mmHg, PP was strongly linked with incident Pre-DM (HR:1.009, 95%CI: 1.008-1.011,
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9 289 P<0.001). However, their correlation was not significant when PP was less than 29 mmHg (HR:
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11 290 0.990, 95%CI: 0.977-1.003, P=0.149).

291 **The results of the subgroup analysis**

292 Interaction tests performed before subgroup analyses showed that age, BMI, gender, family
293 history of diabetes, smoking status, and drinking status interacted with PP (P<0.001)
294 (Supplemental Table 4). We selected age, BMI, gender, family history of diabetes, smoking status,
295 and drinking status as stratification variables and examined the changes in their impact sizes
296 (Supplemental Table 5). Age, drinking status, and family history of diabetes had no impact on the
297 correlation between PP and the risk of prediabetes. Females, never smokers, ever smokers, and
298 subjects with BMI<25 kg/m² were more likely to be associated with prediabetes risk. Conversely,
299 there was a weaker connection in males, current smokers, and individuals with BMI≥25 kg/m².

300 **Discussion**

301 The current study's main goal was to investigate the connection between PP and incident
302 Pre-DM in Chinese participants. The findings demonstrated a correlation between increased PP
303 and a higher risk of prediabetes. The correlation between PP and Pre-DM was also investigated on
304 the left and right sides of the inflection point. PP level and incident prediabetes have a nonlinear
305 relationship. It was found that never-smokers, ever-smokers, females, and individuals with
306 BMI<25 kg/m² had a greater correlation between PP and incident Pre-DM.

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

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4 309 illness, and arterial stiffness[23-28]. In comparison to blood pressure, PP has a better predictive
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6 310 capacity for poor cardiovascular outcomes in people with diabetes, according to several previous
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9 311 pieces of evidence[6, 29]. In addition, some studies found that PP demonstrated strong predictive
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11 312 ability in the homeostatic model assessment of insulin resistance index, diabetes, and metabolic
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14 313 syndrome[30-32]. In a retrospective study involving 211814 Chinese participants, after controlling
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17 314 for BMI, smoking and drinking status, age, TC, gender, family history of diabetes, FPG, TG, and
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20 315 BUN and ALT, Higher PP levels independently connect with increased T2DM risk (HR:1.003,
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22 316 95%CI:1.001,1.005)[11]. In a longitudinal study involving 12272 Chinese, Zhang L et al.[30]
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25 317 found that high PP in Chinese women may be related to the development of T2DM after adjusting
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27
28 318 for confounding covariates. In a national cross-sectional study involving 6187 Korean older
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31 319 adults, Kwon YJ et al.[32] discovered a positive association between PP and metabolic syndrome
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33 320 after adjusting for alcohol consumption, smoking, age, regular exercise, and mean arterial blood
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36 321 pressure. In another cross-sectional cohort study that included 38708 rural Chinese participants,
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39 322 compared with the lowest group, the odds ratio (95%CI) of PP in the highest quartile of risk for
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42 323 metabolic syndrome was found to be 1.81 (1.67-1.95) after controlling for confounders[33]. In
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45 324 addition, in a prospective research enrolling 32917 Chinese, the HR (95%CI) for diabetes in the
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48 325 Q3 and Q4 groups were 1.13 (1.04-1.22) and 1.14 (1.05-1.24), respectively, after adjusting for
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51 326 covariates compared to the Q1 group[34]. However, in a multicenter, longitudinal cohort study
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54 327 that included 18619 adults, high PP was not related to an increased risk of diabetes after adjusting
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57 328 for BMI, mean arterial pressure, gender, high-sensitivity C reactive protein, age, exercise,
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60 329 smoking, blood pressure lowering agents, drinking, hyperlipidemia, and family history of
330 diabetes[35]. A retrospective study of 178 individuals with hypertension found that PP was not

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4 331 associated with the risk of new-onset diabetes after adjusting for potential confounders[36]. This
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6 332 retrospective cohort study involved 182672 Chinese individuals and revealed a higher incidence of
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9 333 prediabetes at increased PP levels. After adjusting for smoking status, BMI, TG, ALT, TC, AST,
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11 334 LDL-C, BUN, HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the
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14 335 results indicated that each unit of the LAP raised the risk of prediabetes by 0.9%. Moreover,
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17 336 sensitivity analysis has demonstrated that this correlation remains observable in Chinese adults
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19 337 with age <60 years or BMI <25 kg/m². The efforts mentioned above have demonstrated the
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22 338 consistency of the connection between PP and Pre-DM risk. The findings offered a clinical
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25 339 PP-level intervention guideline to decrease Pre-DM risk.

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27 340 Few previous studies have investigated the probable curvilinear link between PP and
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30 341 prediabetes. The current study first examined the nonlinear association between PP and
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33 342 prediabetes. After controlling for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN,
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36 343 HDL-C, SCr, sex, FPG, family history of diabetes, drinking status, and age, the findings revealed
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38 344 that the connection between PP and prediabetes was nonlinear. Based on a two-piecewise Cox
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41 345 proportional hazards regression model, we identified the inflection point of PP as 29 mmHg.
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43 346 When PP levels exceeded 29 mmHg, a 1-unit increase in PP correlated with a 0.9% increase in the
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46 347 hazard ratio (HR) for individuals with Pre-DM (HR: 1.009, 95% CI: 1.008-1.011, P<0.001).
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48 348 However, no significant correlation was observed between PP levels below 29 mmHg and the
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51 349 incident Pre-DM (HR: 0.990, 95% CI: 0.977-1.003, P = 0.149). Elevated PP serves as a valuable
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54 350 indicator for identifying high-risk participants likely to develop Pre-DM during follow-up.
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56 351 Moreover, our analysis revealed that the relationship between PP and the emergence of Pre-DM
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59 352 was more pronounced in never-smokers, ever-smokers, females, and individuals with BMI< 25
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4 353 kg/m². In contrast, this association appeared attenuated in males, current smokers, and individuals
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7 354 with BMI \geq 25 kg/m². Prior research has consistently identified obesity, smoking, and male as
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9 355 contributors to insulin resistance[37, 38], which is a precursor to Pre-DM. We postulated that the
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11 356 attenuated association observed in these subgroups may be attributable to the overriding influence
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14 357 of these risk factors on the pathogenesis of Pre-DM. The direct impact of PP on prediabetes risk
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17 358 may be somewhat eclipsed by the more substantial effects of obesity, active smoking, and the
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19 359 male sex on insulin resistance and subsequent Pre-DM development. This information can remind
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22 360 individuals to adopt healthier lifestyle habits sooner, ultimately improving their outcomes.
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25 361 The mechanism behind the association between PP and prediabetes is yet unknown. Several
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27 362 explanations currently exist for PP leading to Pre-DM. Firstly, endothelial cell dysfunction may
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30 363 result in microvascular dysfunction[39], which in turn causes dysfunctional glucose metabolism,
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33 364 insulin resistance, poor tissue perfusion, and arterial stiffness[40-42]. Additionally, arterial
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35 365 stiffness may exacerbate microvascular lesions, creating a vicious cycle[43, 44]. Secondly, normal
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38 366 arteries can reduce PP, but arterial stiffness increases blood flow through low-resistance organs
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41 367 (such as the kidney and brain), which will cause organ dysfunction[45]. As a low-resistance,
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43 368 high-blood-flow organ with a mean tissue perfusion of 250–300 ml/min/100g, the pancreas may
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45 369 be negatively impacted by arterial stiffness in terms of its endocrine function.
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48 370 The current research possesses several notable advantages. Firstly, we delved deeper into the
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51 371 nonlinear relationship between PP and prediabetes. Secondly, we minimized the impact of residual
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53 372 confounding factors through rigorous statistical adjustments. Thirdly, we conducted sensitivity
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56 373 analyses to ensure the robustness of our findings. Lastly, we performed a group analysis to
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59 374 evaluate other potential risk covariates that could affect the link between PP and Pre-DM.
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4 375 The present study has certain limitations. First, this study is based on a Chinese population, and
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6 376 while it offers valuable insights, the findings might not be directly generalizable to other
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9 377 populations due to genetic, lifestyle, and environmental differences. In the future, we will explore
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11 378 the relationship between PP and prediabetes risk in diverse populations. Second, as our study was
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14 379 a secondary analysis, we cannot guarantee data quality monitoring and variable control. In
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17 380 forthcoming research endeavors, we will endeavor to construct prospective cohort studies with
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19 381 enhanced data quality oversight and variable control, thereby mitigating bias. Third, excluding
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22 382 over 500,000 individuals from a final cohort of 182,672 subjects could have selection bias and
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25 383 implications for generalisability. In the future, we will design prospective studies in a more
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27 384 diverse population to validate our findings. Fourth, prediabetes was defined based on impaired
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30 385 fasting glucose levels in our study. This could potentially lead to underestimation of prediabetes
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33 386 incidence. This is a secondary retrospective study, and the raw data did not provide information
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36 387 regarding 2-hour oral glucose tolerance test or glycosylated hemoglobin level measurements. In
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38 388 the future, we will consider designing our study to document more variables, including 2-hour oral
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41 389 glucose tolerance test or glycosylated hemoglobin level measurements. Fifth, as with all
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44 390 observational studies, there may be uncontrolled or unmeasured confounding factors, such as diet,
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47 391 exercise, atherosclerosis, the use of antihypertensive medications, and the presence of
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50 392 hypertension, despite controlling for known potential confounders like BMI, TC, LDL-C, AST,
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53 393 ALT, Scr, BUN, and FPG. However, we used the E-value to evaluate the impact of unmeasured
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56 394 confounders and determined it unlikely that they fully explained the results. Sixth, SBP and DBP
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59 395 were only measured at baseline in the original study, and we did not assess how SBP and DBP
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396 changed over time. In the future, we will consider designing our own study and documenting more

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4 397 information, such as diet, exercise, atherosclerosis, antihypertensive medications, the presence of
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6 398 hypertension and changes in blood pressure over time, and then utilizing a GAM model to explore
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9 399 the impact of changes in PP on Pre-DM risk.

400 **Conclusion**

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

407 **Declarations**

408 **Ethics approval and consent to participate**

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

413 **Consent for publication**

414 Not applicable.

415 **Availability of data and materials**

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

418 **Competing interests**

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4 419 The authors declare that they have no competing interests.
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18 19 425 **Author contributions**

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22 426 Changchun Cao and Yong Han contributed to the study concept and design, researched and
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25 427 interpreted the data, and drafted the manuscript. Haofei Hu, Yongcheng He, and Jiao Luo
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28 428 analyzed the data and reviewed the manuscript. Changchun Cao and Yong Han oversaw the
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31 429 project's progress, contributed to the discussion, and reviewed the manuscript. Haofei Hu,
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33 430 Yongcheng He, and Jiao Luo were the guarantors of this work. As such, they had full access to all
34
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36 431 data in the study and were responsible for the data integrity and analysis accuracy. All authors
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38 432 read and approved the final manuscript.

39 40 433 **Acknowledgments**

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441 **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

442 Values are n (%) or mean ± SD

443 PP: pulse pressure, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, ALT

444 alanine aminotransferase, AST aspartate aminotransferase, HDL-C high-density lipoprotein cholesterol, LDL-C

445 low-density lipoprotein cholesterol, TC total cholesterol, TG triglycerides, Scr serum creatinine, BUN blood urea

446 nitrogen, FPG fasting plasma glucose

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454 **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) <0.001	1.070 (1.024, 1.118) 0.003	1.043 (0.998, 1.090) 0.061	1.046 (1.001, 1.093) 0.045
Q3	1.347 (1.290, 1.407) <0.001	1.208 (1.156, 1.262) <0.001	1.131 (1.083, 1.181) <0.001	1.129 (1.080, 1.179) <0.001
Q4	1.860 (1.787, 1.935) <0.001	1.408 (1.352, 1.467) <0.001	1.246 (1.197, 1.298) <0.001	1.238 (1.188, 1.291) <0.001
P for trend	<0.001	<0.001	<0.001	<0.001
Gender				
Male		ref	ref	
Female		0.777 (0.751, 0.803) <0.001	0.877 (0.843, 0.913) <0.001	
Age(years)		1.027 (1.026, 1.028) <0.001	1.022 (1.021, 1.023) <0.001	
Drinking status				
Current-drinker		ref	ref	
Ex-drinker		0.965 (0.877, 1.061) 0.457	1.013 (0.920, 1.114) 0.799	
Never- drinker		0.911 (0.832, 0.997) 0.042	1.075 (0.981, 1.178) 0.122	
Smoking status				
Current-smoker		ref	ref	
Ex-smoker		1.020 (0.948, 1.097) 0.596	1.021 (0.949, 1.098) 0.578	
Never-smoker		1.055 (1.016, 1.095) 0.005	1.023 (0.985, 1.062) 0.246	
Family history of diabetes				
No		ref	ref	
Yes		1.157 (1.058, 1.265) 0.001	1.120 (1.024, 1.225) 0.013	
BMI (kg/m ²)		1.091 (1.086, 1.095) <0.001	1.060 (1.055, 1.065) <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

455 Crude model: we did not adjust for other covariants.
 456 Minimally-adjusted model: we adjusted for gender, age, family history of diabetes, drinking status, smoking status, and BMI.
 457 Fully-adjusted model: we adjusted for gender, age, family history of diabetes, drinking status, smoking status, BMI, TC, TG,
 458 HDL-C, LDL-C, AST, ALT, SCr, BUN, and FPG.
 459 GAM: All covariates listed in Table 1 were adjusted. However, continuous covariates were adjusted as nonlinearity.
 460 HR, hazard ratios; CI, confidence interval; Ref, reference; GAM, generalized additive mode; PP, pulse pressure.

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485 **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	

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

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

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4 516 **Figure 1** Study Population
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6 517 **Figure 2** The nonlinear relationship between PP and incident prediabetes. A
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9 518 nonlinear relationship between PP and incident prediabetes was detected after
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12 519 adjusting for smoking status, BMI, TG, ALT, TC, AST, LDL-C, BUN, HDL-C, SCr,
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14 520 sex, FPG, family history of diabetes, drinking status, and age.
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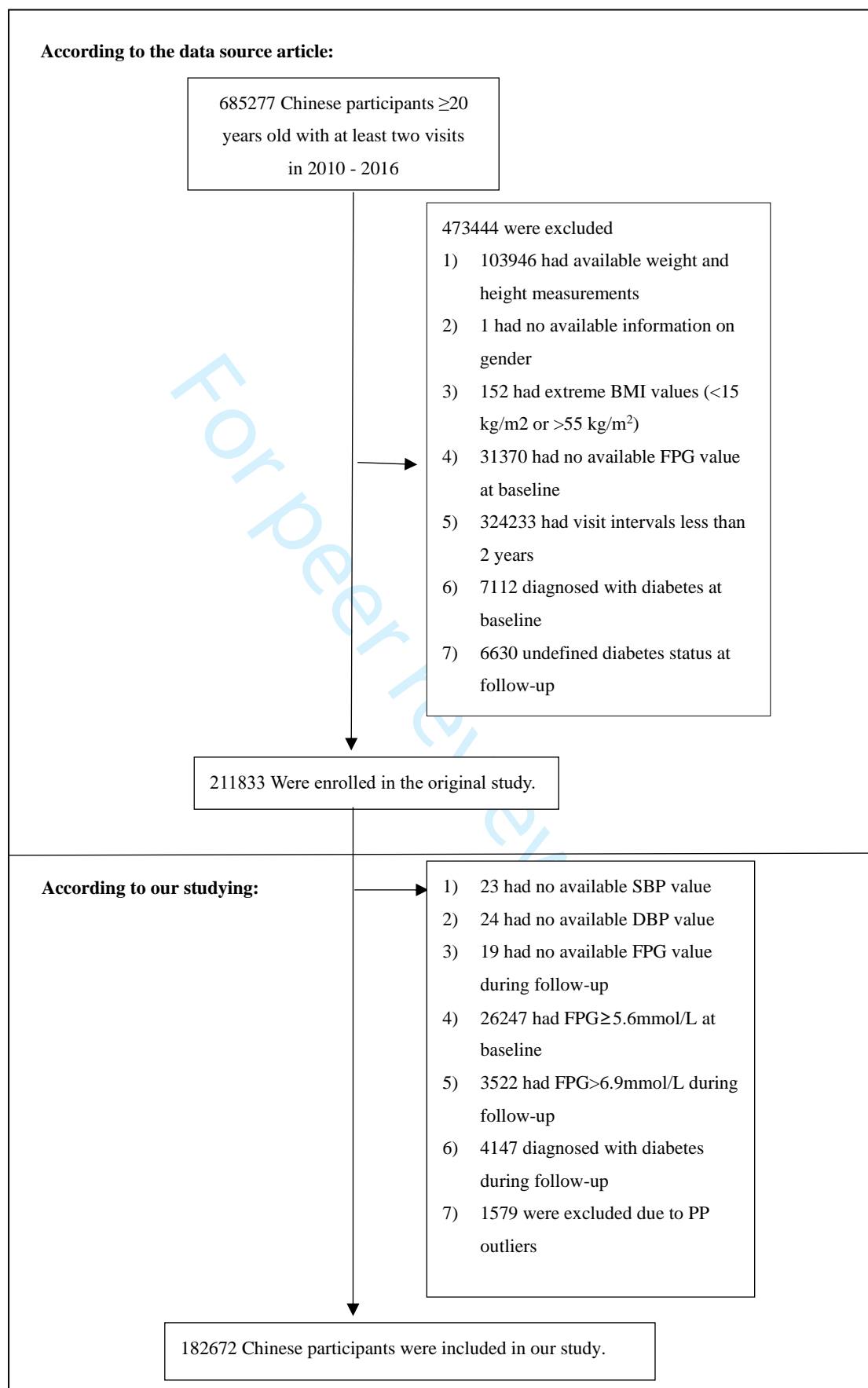
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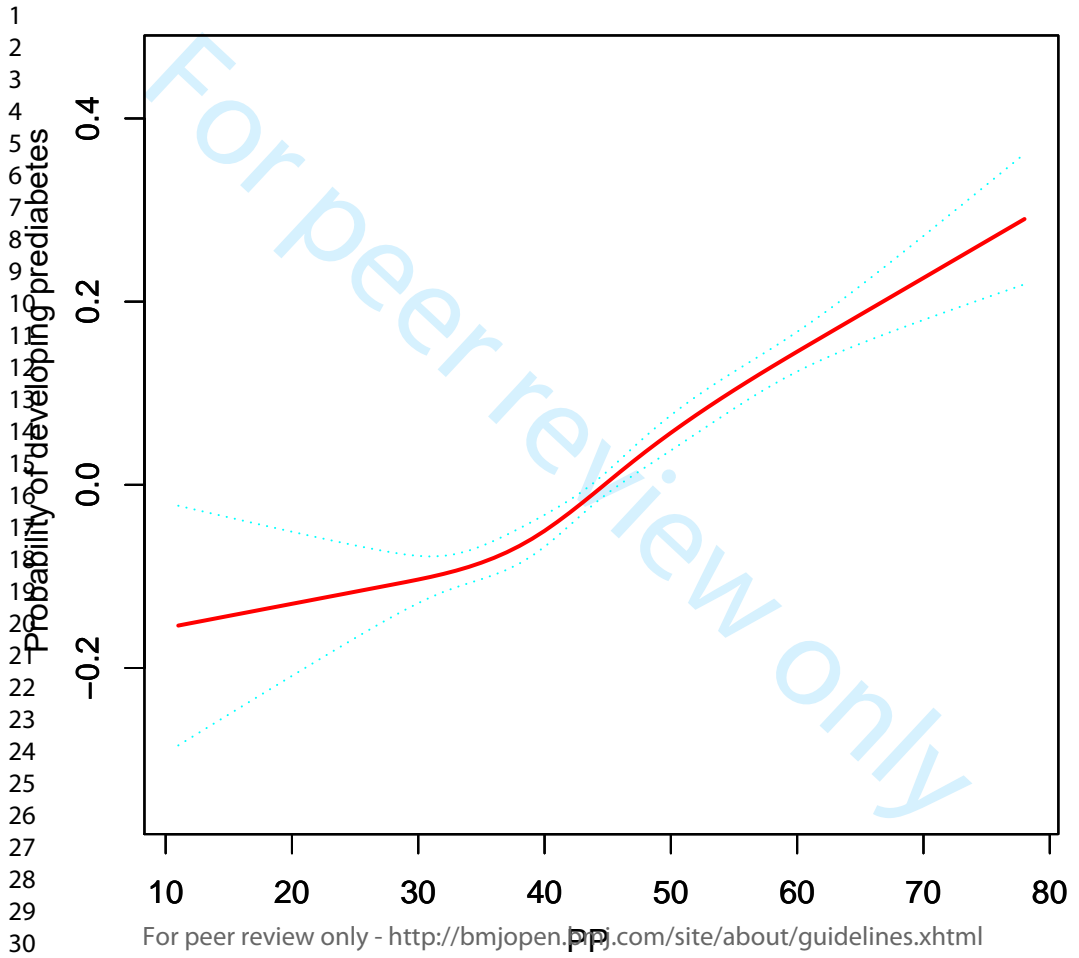
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Supplemental Table 1 Incidence rate of incident prediabetes.

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/m ²)	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 \geq 25kg/m². 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 \geq 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

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

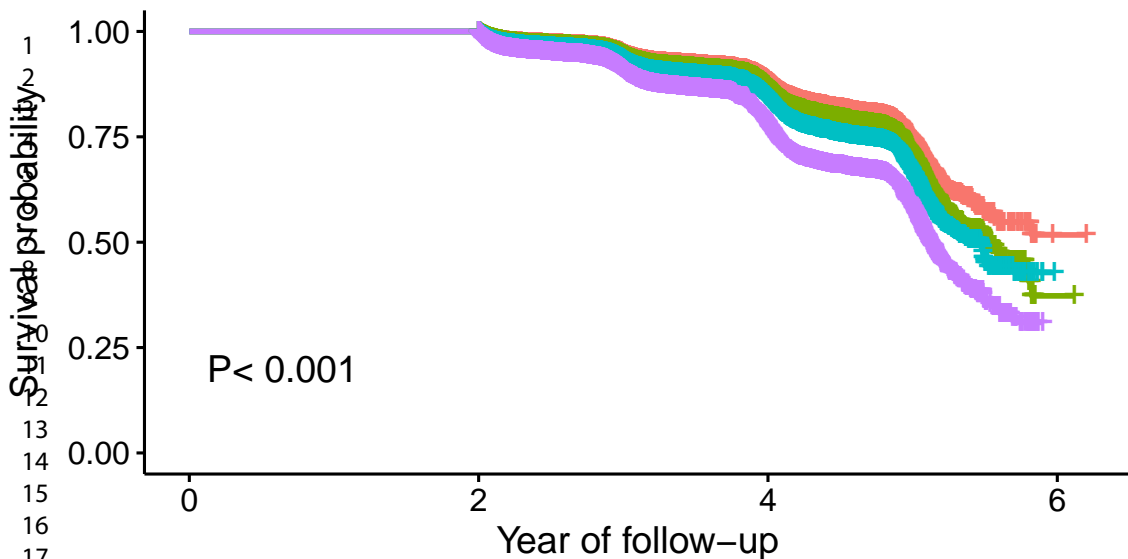
Characteristic	No of participants	HR (95%CI)	P value	P for interaction
Age, years				0.134
<60	165813	1.008 (1.006, 1.009)	<0.001	
≥60	16859	1.010 (1.007, 1.013)	<0.001	
Gender				<0.001
Male	96966	1.006 (1.004, 1.008)	<0.001	
Female	85706	1.011 (1.009, 1.013)	<0.001	
BMI (kg/m ²)				<0.001
<25	135554	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
FBG (mmol/L)	4.765 ± 0.487	4.765 ± 0.487	1.000



Number at risk

	0	2	3	4	5	6
PP	39914	21231	9935	2027	1	
Q1	47771	24322	10844	2155	1	
Q2	43811	21525	9281	1760	0	
Q3	51176	24666	10207	2058	0	

Year of follow-up

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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10-11
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

1	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
2			(b) Report category boundaries when continuous variables were categorized	12
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
4				
5	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
6				
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11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	13-14
13	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
14	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
15	Generalisability	21	Discuss the generalisability (external validity) of the study results	16
16				
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21	Other information			
22	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
23				
24				
25				

*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>.