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Association of mean arterial pressure with 5-year risk of incident diabetes in Chinese adults：a secondary population-based cohort study

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ABSTRACT

Objective Hypertension predicts the development of diabetes. However, there are still lacking high-quality studies on the correlation between mean arterial pressure (MAP) and incident diabetes. We aimed to explore the relationship between MAP and diabetes in Chinese adults.

Design This is a secondary retrospective cohort study and the data were downloaded from the 'DATADRYAD' database (www.Datadryad.org).

Participants The study included 210 418 adults without diabetes at baseline between 2010 and 2016 across 32 sites and 11 cities in China.

Setting The target-independent and dependent variables were MAP measured at baseline and diabetes occurred during follow-up. Cox proportional hazards regression was used to explore the relationship between MAP and diabetes.

Primary outcome measures The outcome was incident diabetes, which was defined as fasting blood glucose ≥7.00 mmol/L and/or self-reported diabetes during follow-up. Patients were censored either at the time of the diagnosis or at the last visit, whichever comes first.

Results 3927 participants developed diabetes during a 5-year follow-up. After adjusting covariates, MAP positively correlated with diabetes (HR=1.008, 95% CI 1.005 to 1.011, p<0.001), and the absolute risk difference was 0.02%. E-value analysis and multiple imputations were used to explore the robustness of the results. The relationship between MAP and diabetes was also non-linear, and the inflection point of MAP was 100.333 mm Hg. Subgroup analysis revealed a stronger association between MAP and diabetes in people with age (≥30,<50 years old), fasting plasma glucose <6.1 mmol/L and drinking. Additionally, receiver operating characteristic (ROC) curves showed the predictive performance of MAP for diabetes was similar to systolic blood pressure (SBP) (area under the curve (AUC)=0.694 with MAP vs AUC=0.698 with SBP).

Conclusions MAP is an independent predictor for a 5-year risk of incident diabetes among Chinese adults. The relationship between MAP and diabetes is also non-linear. When MAP is below 100.333 mm Hg, MAP is closely positively related to diabetes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our research sample was large and participants were from multiple centres, well representative of the Chinese population.
⇒ We expounded a non-linear relationship, and it is the first study to identify the inflection point of mean arterial pressure's effect on diabetes.
⇒ The subgroup analysis helped us explore other potential risks in the association between mean arterial pressure and incident diabetes.
⇒ The researchers did not perform a 2-hour oral glucose tolerance test or measure glycosylated haemoglobin level, which may underestimate the incidence of diabetes.

INTRODUCTION

The worldwide incidence of diabetes mellitus has increased significantly. Diabetes has emerged as a major epidemic in China. According to an extensive, nationally representative survey of Chinese adults, the estimated overall prevalence of diabetes had risen to be 10.9% in 2013.[1] Diabetes has become one of the important public health issues that causes disability and premature death. It is a debilitating disease with potentially various complications, which reduces the quality of life and causes serious socioeconomic effects. Thence, identifying risk factors of incident diabetes is critical to prevent diabetes.

It is well known that hypertension and diabetes frequently coexist. Some researchers revealed that hypertension was closely related to impaired glucose tolerance and diabetes mellitus.[2–4] A Chinese study showed that high blood pressure was positively related to incident diabetes.[5] Some studies explored that elevated systolic blood pressure (SBP) levels by 1 mm Hg were associated with a 0.6%–4.0% increased risk of type 2 diabetes mellitus (T2DM).[6–11] Similar findings showed that a 1 mm Hg increase in diastolic blood pressure

(DBP) levels increased the risk of new-onset diabetes by 5.2%.[12] SBP is the maximum pressure exerted on the arterial wall caused by the contraction of the ventricle, and DBP is the lowest pressure in the artery measured during ventricular relaxation.[13] However, mean arterial pressure (MAP) is the average blood pressure throughout a cardiac cycle. Besides, MAP is the steady flow of blood through the aorta and its arteries, and MAP reflects peripheral resistance and cardiac output.[14] In addition, MAP is a composite blood pressure index that considers SBP, DBP and pulse pressure (PP). Therefore, MAP can reflect blood pressure status more comprehensively. However, there were only a few studies that have assessed the relationship between MAP and incident diabetes. A rural Chinese cohort study demonstrated that MAP was positively correlated with T2DM in Chinese women.[15] Moreover, two studies in Cameroon and Iran revealed that MAP was as strong a predictor of diabetes as SBP and DBP.[16 17] Considering their small sample size and ethnic differences, we conducted the study to explore the potential relationship between MAP and incident diabetes in a large cohort of Chinese adults across 32 sites and 11 cities.

METHODS

Data source, participants

The data of all participants were downloaded for free from the 'DATADRYAD' database (www.Datadryad.org). The raw data were provided by Chen *et al*,[18] and the participant records were fully anonymised before we accessed them. The original study enrolled 685 277 adult Chinese persons >20 years old with at least two visits between 2010 and 2016 across 32 sites and 11 cities in China. Variables were as follows: age, gender, body mass index (BMI), DBP, SBP, fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), serum creatinine (Scr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), smoking and drinking status, family history of diabetes, year of follow-up and censor of diabetes at follow-up. In our research, we added MAP and PP. Participants were excluded at baseline in the original study, as follows: (1) no available information on weight, height and gender, (2) extreme BMI values (<15 kg/m^2 or >55 kg/m^2), (3) visit intervals <2 years, (4) no available FPG value, (5) participants diagnosed with diabetes at baseline and participants with undefined diabetes status at follow-up. We further excluded participants with incomplete blood pressure (n=24). To reduce interference, we excluded those whose MAP was below means minus three SD or more than means plus three SD (n=1391).[19] Finally, 210 418 subjects were included in the secondary analysis.

Study design

The original study documented the design of the study.[18] All subjects were required to do a questionnaire about demographics and lifestyle when they visited the health check-up centre. Trained staff measured their height and weight. Weight was measured in light clothing without shoes to the nearest 0.1 kg. The height is accurate to 0.1 cm. BMI was equal to the weight divided by the square of height, which is accurate to 0.1 kg/m^2. Fasting venous blood samples were collected after fasting at least 10 hours after each visit. An automatic analyser measured FPG, Scr, TC, TG, HDL-C, LDL-C, ALT and AST. The staff used a standard mercury sphygmomanometer to measure their blood pressure. MAP and PP were calculated as MAP=1/3 SBP +2/3 DBP and PP=SBP–DBP.[20] The data were collected under standardised conditions and carried out by trained staff in accordance with uniform procedures. Laboratory methods were carefully standardised through strict internal and external quality control. The target independent and dependent variables were MAP measured at baseline and incident diabetes during follow-up, respectively. As a retrospective cohort study, it decreased the risk of selection bias and observation bias.

Diagnosis criteria

The definitions of diabetes were fasting blood glucose ≥7.00 mmol/L and/or self-reported diabetes during follow-up. Patients were censored either at the time of the diagnosis or at the last visit, whichever comes first.

Patient and public involvement

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

Statistical analysis

First, we dealt with the missing values of covariates. Missing continuous variables were mainly supplemented by means or median. Since the missing values of HDL-C, LDL-C and AST were about 50%, we converted them as categorical variables based on the tertiles. And the missing categorical variables in each covariate were considered as a group.

Next, we analysed the baseline characteristics of participants. All participants were arranged into four groups, including low MAP group (MAP <80 mm Hg), medium MAP group (80≤MAP<90 mm Hg), high MAP group (90≤MAP<100 mm Hg) and very high MAP group (MAP ≥100 mm Hg). Continuous variables were described as the means±SDs (normal distribution) or medians (quartiles) (skewed distribution), and categorical variables were described as frequency or percentages. We tested differences between means and proportions of the groups based on the one-way ANOVA (analysis of variance) test for normally distributed quantitative variables, the Kruskal-Wallis H test for skewed quantitative variables and the χ^2 test for categorical variables.[21] Third, we calculated the person-years of follow-up from the first visit to the time of the diagnosis of diabetes or at the last visit, whichever came first.[15] Person-years incidence and cumulative incidence were applied to describe the incidence rate.[22] Cox proportional hazard regression

models were used to detect the predictive role of MAP on the risk of diabetes. The results from unadjusted, minimally adjusted analyses and fully adjusted analyses were presented simultaneously in our study. The strategy for selecting covariates to adjust was mainly based on clinical experience, literature reports and statistical methods. The principle of statistical methods is that we adjusted the covariances which changed the matched HR by more than 10%.[23] In the minimally adjusted model, we adjusted for the demographic covariates, including age, gender, BMI, family history of diabetes, smoking and drinking status. In fully adjusted model, we adjusted for all demographics and biochemical covariates, including age, gender, BMI, family history of diabetes, smoking and drinking status, FPG, TC, TG, HDL-C, LDL-C, ALT, AST and Scr. Additionally, we calculated the absolute risk difference (ARD). To do sensitivity analysis, we treated MAP as a categorical variable to explore the relationship between MAP level and incident diabetes. We explored the potential for unmeasured confounding between MAP and diabetes by calculating E-values.[24] To ensure the robustness of results, multiple imputations were also used to replace the missing values to reduce the bias caused by missing covariables.[25] The results of multiple regression analysis in this study adopted the values of imputed data, in which the estimates from each imputation were combined according to Rubin's rules.[26] Given that MAP was a continuous variable, we also verify the non-linear correlation of MAP and incident diabetes by using a generalised additive model (GAM). If the relationship was non-linear, from the perspective of a smoothing plot, a two-stage linear regression model would calculate the threshold effect of the MAP on diabetes. If there was an evident relationship between MAP and diabetes, it would calculate the inflection point. Moreover, the Cox proportional hazard models were used to do subgroup analysis (age, gender, BMI, FPG, HDL-C, LDL-C, family history of diabetes, smoking and drinking status). According to the clinical cut point or binary, the continuous variables were converted to categorical variables. Each stratification has undergone a fully adjusted analysis, except for the stratification factor itself. The likelihood ratio test was used to examine the modifications and interactions of subgroups. The Kaplan-Meier method was used to compare survival estimates and cumulative event rates. And the log-rank test was conducted to compare the Kaplan-Meier HRs for adverse events. The impact of SBP, DBP, PP and MAP on incident diabetes was evaluated by the receiver operating characteristics (ROC) curve.

Statistical analyses were done by the statistical software package R (http://www.R-project.org, The R Foundation) and Empower-Stats (http://www.empowerstats.com, X&Y Solutions, Boston, MA). The tests were two-tailed, and p<0.05 was statistically significant.

RESULTS

Our study included a total of 210 418 participants (54.7% men and 45.3% women). The mean age of all participants was 42.0±12.6 years old. During the 5-year follow-up period, 3927 participants developed diabetes. The mean SBP, DBP, PP and MAP were 118.7±15.8 mm Hg, 73.9±10.4 mm Hg, 44.8±11.6 mm Hg, 88.9±11.2 mm Hg, respectively. The mean FPG was 4.9±0.6 mmol/L. The number of participants with the missing value of TC, TG, HDL-C and LDL-C was 4854, 4887, 94 000 and 92874, respectively. Besides, the missing value of Scr, ALT and AST was 11173, 1782 and 122458, respectively. In addition, the missing value of smoking and drinking status was 150 497 and 150 497, respectively.

Baseline characteristics of participants

Table 1 illustrated basic clinical measurements, biochemical tests and other parameters of the participants. We divided participants into four groups, including low MAP group (MAP <80 mm Hg), medium MAP group (80≤MAP<90 mm Hg), high MAP group (90≤MAP<100 mm Hg) and very high MAP group (MAP ≥100 mm Hg). The results showed that in the very high MAP group, the subjects had higher age, BMI, SBP, DBP, PP, MAP, FPG, Scr, TC, TG, ALT, AST and more current smoker and drinker. Besides, fewer participants at high HDL-C level in the very high MAP group and more participants at high LDL-C level. In addition, the low MAP group (MAP <80 mm Hg) had a higher incidence of family history of diabetes.

The incidence rate of incident diabetes

Table 2 revealed that 3927 participants developed diabetes during a 5-year follow-up. The total incidence rate of diabetes was 598.78 per 100 000 person-years. Specifically, the incidence rates of the four MAP groups were 190.02, 360.74, 698.40 and 1354.31 per 100 000 person-years, respectively. Compared with the low MAP group, participants with increased MAP levels had a higher cumulative incidence. The cumulative incidence of total incident diabetes and each of the MAP groups was 1.854% (1.797%–1.911%), 0.590% (0.521%–0.659%), 1.125% (1.047%–1.203%), 2.185% (2.065%–2.304%) and 4.209% (3.999%–4.418%), respectively.

Univariate analysis

Table 3 demonstrated a positive association between age, BMI, SBP, DBP, PP, MAP, FPG, Scr, TC, TG, LDL-C, ALT, AST, family history of diabetes, smoking, drinking and incident diabetes. In contrast, HDL-C negatively correlated with incident diabetes. Meanwhile, men had a higher risk of developing diabetes than women.

Figure 1 described the results of Kaplan-Meier curves of the cumulative hazards. The risk of developing diabetes was different between the four MAP groups (log-rank test, p<0.001). With the increase in MAP level, the cumulative risk of diabetes gradually increased. Thus, the very high MAP group faced the maximum risk of diabetes.

Table 1 The baseline characteristics of participants

MAP group	Low MAP group (MAP <80 mm Hg)	Medium MAP group (80≤MAP<90 mm Hg)	High MAP group (90≤MAP<100 mm Hg)	Very high MAP group (MAP ≥100 mm Hg)	P value
Participants	47 430	70 126	57 530	35 332	
Age (years)	38.30±9.74	39.96±11.33	43.17±13.21	49.20±14.12	<0.001
Gender					<0.001
Male	14 926 (31.47%)	37 150 (52.98%)	38 008 (66.07%)	25 017 (70.81%)	
Female	32 504 (68.53%)	32 976 (47.02%)	19 522 (33.93%)	10 315 (29.19%)	
BMI (Kg/m^2)	21.60±2.73	22.77±3.08	23.91±3.29	25.12±3.37	<0.001
SBP (mm Hg)	100.88±7.28	113.80±7.63	125.70±8.29	141.09±11.76	<0.001
DBP (mm Hg)	61.60±4.44	70.47±4.13	78.81±4.58	89.45±6.48	<0.001
PP (mm Hg)	39.28±8.32	43.32±10.10	46.89±11.38	51.64±13.82	<0.001
MAP (mm Hg)	74.69±3.93	84.92±2.85	94.44±2.85	106.66±5.62	<0.001
FPG (mmol/L)	4.75±0.55	4.87±0.58	4.98±0.62	5.11±0.66	<0.001
Scr (umol/L)	64.99±13.89	69.61±14.93	72.38±15.12	73.78±16.38	<0.001
TC (mmol/L)	4.51±0.83	4.64±0.86	4.78±0.90	4.96±0.93	<0.001
TG (mmol/L)	0.84 (0.61–1.17)	1.01 (0.71–1.46)	1.19 (0.83–1.77)	1.41 (1.00–2.09)	<0.001
HDL-C (mmol/L)					<0.001
Low	6775 (14.28%)	12 260 (17.48%)	11 615 (20.19%)	7884 (22.31%)	
Medium	8399 (17.71%)	12 574 (17.93%)	10 317 (17.93%)	6688 (18.93%)	
High	10 777 (22.72%)	13 261 (18.91%)	9696 (16.85%)	6172 (17.47%)	
Not recorded	21 479 (45.29%)	32 031 (45.68%)	25 902 (45.02%)	14 588 (41.29%)	
LDL-C (mmol/L)					<0.001
Low	10 722 (22.61%)	13 561 (19.34%)	9421 (16.38%)	5163 (14.61%)	
Medium	8756 (18.46%)	12 905 (18.40%)	10 658 (18.53%)	6854 (19.40%)	
High	6559 (13.83%)	11 912 (16.99%)	11 938 (20.75%)	9095 (25.74%)	
Not recorded	21 393 (45.10%)	31 748 (45.27%)	25 513 (44.35%)	14 220 (40.25%)	
ALT (U/L)	14.20 (11.00–20.10)	17.20 (12.40–25.90	20.00 (14.30–31.00)	22.60 (16.00–34.00)	<0.001
AST (U/L)					<0.001
Low	9198 (19.39%)	10 381 (14.80%)	6586 (11.45%)	3158 (8.94%)	
Medium	6386 (13.46%)	9877 (14.08%)	8166 (14.19%)	4794 (13.57%)	
High	4126 (8.70%)	8869 (12.65%)	9409 (16.35%)	7010 (19.84%)	
Not recorded	27 720 (58.44%)	40 999 (58.46%)	33 369 (58.00%)	20 370 (57.65%)	
Smoking status					<0.001
Current smoker	1563 (3.30%)	3856 (5.50%)	3982 (6.92%)	2576 (7.29%)	
Ever smoker	339 (0.71%)	839 (1.20%)	861 (1.50%)	507 (1.43%)	
Never smoker	9831 (20.73%)	15 600 (22.25%)	13 006 (22.61%)	6961 (19.70%)	
Not recorded	35 697 (75.26%)	49 831 (71.06%)	39 681 (68.97%)	25 288 (71.57%)	
Drinking status					<0.001
Current drinker	126 (0.27%)	345 (0.49%)	467 (0.81%)	391 (1.11%)	
Ever drinker	1193 (2.52%)	3040 (4.34%)	3043 (5.29%)	1635 (4.63%)	
Never drinker	10 414 (21.96%)	16 910 (24.11%)	14 339 (24.92%)	8018 (22.69%)	
Not recorded	35 697 (75.26%)	49 831 (71.06%)	39 681 (68.97%)	25 288 (71.57%)	
Family history of diabetes					<0.001
No	46 324 (97.67%)	68 599 (97.82%)	56 411 (98.05%)	34 753 (98.36%)	
Yes	1106 (2.33%)	1527 (2.18%)	1119 (1.95%)	579 (1.64%)	

Values are n (%) or mean±SD.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipid cholesterol; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; Scr, serum creatinine; TC, total cholesterol; TG, triglyceride.

Table 2 Incidence rate of incident diabetes

MAP (mm Hg)	Participants (n)	DM events (n)	Cumulative incidence (95% CI)	Per 100 000 person-year
Total	210 418	3927	1.854% (1.797% to 1.911%)	598.78
MAP group				
Low MAP group (MAP <80 mm Hg)	47 430	280	0.590% (0.521% to 0.659%)	190.02
Medium MAP group (80≤MAP<90 mm Hg)	70 126	789	1.125% (1.047% to 1.203%)	360.74
High MAP group (90≤MAP<100 mm Hg)	57 530	1257	2.185% (2.065% to 2.304%)	698.40
very high MAP group (MAP ≥100 mm Hg)	35 332	1487	4.209% (3.999% to 4.418%)	1354.31

DM, diabetes mellitus; MAP, mean arterial pressure.

The results of the relationship between MAP and incident diabetes

Table 4 showed the Cox proportional hazard regression model, which assessed the relationship between MAP and incident diabetes. We simultaneously presented the non-adjusted and two adjusted models. In non-adjusted model, MAP was positively correlated with diabetes (HR=1.059, 95% CI 1.057 to 1.062, p<0.001), and the ARD was 0.09%. In the minimally adjusted model (model I), we adjusted for the demographic covariates, including age, gender, BMI, SBP, DBP, family history of diabetes, smoking and drinking status, the results did not change significantly (HR: 1.018, 95% CI 1.015 to 1.021, p<0.001), and the ARD was 0.02%. In the fully adjusted model (model II), we adjusted for all demographics and biochemical covariates extracted from the raw data, including age, gender, BMI, FPG, TC, TG, HDL-C, LDL-C, ALT, AST, Scr, family history of diabetes, smoking and drinking status. We found that the relationship still exists (HR=1.008, 95% CI 1.005 to 1.011, p<0.001), and the ARD was 0.02%. The results showed that for every 1 mmHg increased in MAP, the risk of diabetes increased by 0.8%.

Sensitivity analysis

We converted MAP into a categorical variable. Compared with the low MAP group in the full model, the risk of diabetes increased by 26.5%, and the absolute risk difference was 0.72% increased in the very high MAP group. In addition, as the level of MAP increases, the risk of diabetes increased accordingly (table 4). Besides, we generated an E-value to assess the sensitivity to unmeasured confounding. The E-value was 1.10. The E-value was greater than the RR of unmeasured confounders and incident diabetes, suggesting unmeasured or unknown confounders had little effect on the relationship between MAP and diabetes. After replacing the missing values through multiple imputations, the relationship between MAP and incident diabetes did not change (HR=1.008, 95% CI 1.005 to 1.011, p<0.001) (Supplementary file). The results showed that our findings were robust.

The analysis of the non-linear relationship

We established a GAM to verify the non-linearity in the association between MAP and incident diabetes (figure 2). The result showed a non-linear relationship between MAP and diabetes (after adjusting for age, gender, BMI, TC, TG, HDL-C, LDL-C, ALT, AST, Scr, family history of diabetes, smoking and drinking status). According to a two-piecewise linear regression model, we found that the inflection point of MAP was 100.333 mm Hg (log-likelihood ratio test p<0.001). When MAP was less than 100.333 mm Hg, MAP was positively related to diabetes (HR:1.022, 95% CI 1.017 to 1.027, p<0.001). In contrast, when MAP was more than 100.333 mm Hg, their relationship tended to be saturated (HR: 1.005, 95% CI 0.998 to 1.012, p=0.163) (table 5).

The results of subgroup analysis

We performed a subgroup analysis to detect other potential risks of the relationship between MAP and incident diabetes. We treated age, gender, BMI, FPG, HDL-C, LDL-C, family history of diabetes, smoking and drinking status as the stratification variables to evaluate the trend of effect sizes in these variables. Table 6 showed that age, FPG and drinking could modify the relationship between MAP and diabetes (all p values for interaction <0.05). We found a stronger association in the population with age (≥30,<50 years old) (HR=1.021, 95% CI 1.011 to 1.030, p<0.001), FPG <6.1 mmol/L (HR=1.016, 95% CI 1.012 to 1.020, p<0.001) and drinking (current drinker: HR=1.029, 95% CI 0.998 to 1.060, p=0.063; ever drinker: HR=1.018, 95% CI 1.002 to 1.034, p=0.025).

Cut-off point of blood pressure for predicting incident diabetes

We analysed the performances and optimal value of cut-off point of various blood pressure indices for predicting incident diabetes, including SBP, DBP, PP and MAP. Our results supported that all four blood pressure indices were associated with the risk of diabetes. Areas under the ROC curves were 0.698 (95% CI 0.690 to 0.707) for SBP, 0.694 (95% CI 0.686 to 0.702) for MAP, 0.658 (95% CI 0.650 to 0.667) for DBP and 0.622 (95% CI 0.612 to

Table 3 The results of univariate analysis

	Statistics	HR (95% CI)	P value
Age (years)	42.018±12.603	1.066 (1.063 to 1.068)	<0.001
Gender			
Male	115 101 (54.701%)	1.0	
Female	95 317 (45.299%)	0.499 (0.465 to 0.535)	<0.001
BMI (Kg/m^2)	23.214±3.330	1.236 (1.227 to 1.245)	<0.001
SBP (mm Hg)	118.722±15.827	1.043 (1.041 to 1.044)	<0.001
DBP (mmHg)	73.937±10.397	1.050 (1.047 to 1.053)	<0.001
PP (mmHg)	44.784±11.563	1.041 (1.038 to 1.043)	<0.001
MAP (mmHg)	88.866±11.218	1.059 (1.057 to 1.062)	<0.001
FPG (mmol/L)	4.913±0.610	10.821 (10.336 to 11.329)	<0.001
Scr (umol/L)	70.027±15.329	1.006 (1.005 to 1.007)	<0.001
TC (mmol/L)	4.704±0.889	1.429 (1.387 to 1.472)	<0.001
TG (mmol/L)	1.328±1.015	1.263 (1.251 to 1.275)	<0.001
HDL-C (mmol/L)			
Low	38 534 (18.313%)	1.0	
Medium	37 978 (18.049%)	0.873 (0.795 to 0.959)	0.005
High	39 906 (18.965%)	0.781 (0.709 to 0.860)	<0.001
Not recorded	94 000 (44.673%)	0.585 (0.539 to 0.634)	<0.001
LDL-C (mmol/L)			
Low	38 867 (18.471%)	1.0	
Medium	39 173 (18.617%)	1.134 (1.023 to 1.258)	0.017
High	39 504 (18.774%)	1.672 (1.519 to 1.841)	<0.001
Not recorded	92 874 (44.138%)	0.791 (0.720 to 0.868)	<0.001
ALT (U/L)	23.855±22.007	1.004 (1.004 to 1.005)	<0.001
AST (U/L)			
Low	29 323 (13.936%)	1.0	
Medium	29 223 (13.888%)	1.424 (1.239 to 1.636)	<0.001
High	29 414 (13.979%)	2.798 (2.467 to 3.173)	<0.001
Not recorded	122 458 (58.197%)	1.368 (1.217 to 1.538)	<0.001
Smoking status			
Current smoker	11 977 (5.692%)	1.0	
Ever smoker	2546 (1.210%)	0.813 (0.628 to 1.051)	0.113
Never smoker	45 398 (21.575%)	0.449 (0.395 to 0.511)	<0.001
Not recorded	150 497 (71.523%)	0.596 (0.535 to 0.665)	<0.001
Drinking status			
Current drinker	1329 (0.632%)	1.0	<0.001
Ever drinker	8911 (4.235%)	0.484 (0.346 to 0.677)	
Never drinker	49 681 (23.611%)	0.482 (0.355 to 0.655)	<0.001
Not recorded	150 497 (71.523%)	0.510 (0.377 to 0.689)	<0.001
Family history of diabetes			
No	206 087 (97.942%)	1.0	
Yes	4331 (2.058%)	1.733 (1.477 to 2.033)	<0.001

Values are n (%) or mean±SD.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipid cholesterol; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; Scr, serum creatinine; TC, total cholesterol; TG, triglyceride.

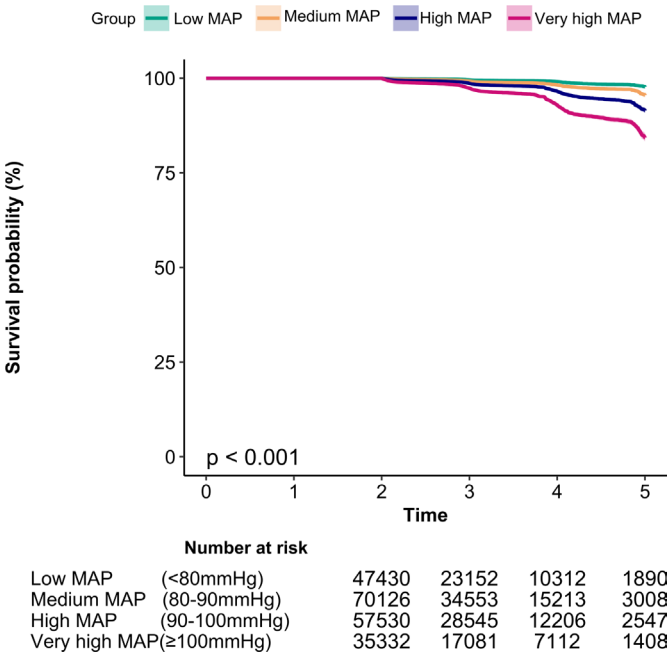

Figure 1 Kaplan-Meier event-free survival curve of incident diabetes based on MAP groups (log-rank, p<0.001). MAP, mean arterial pressure.

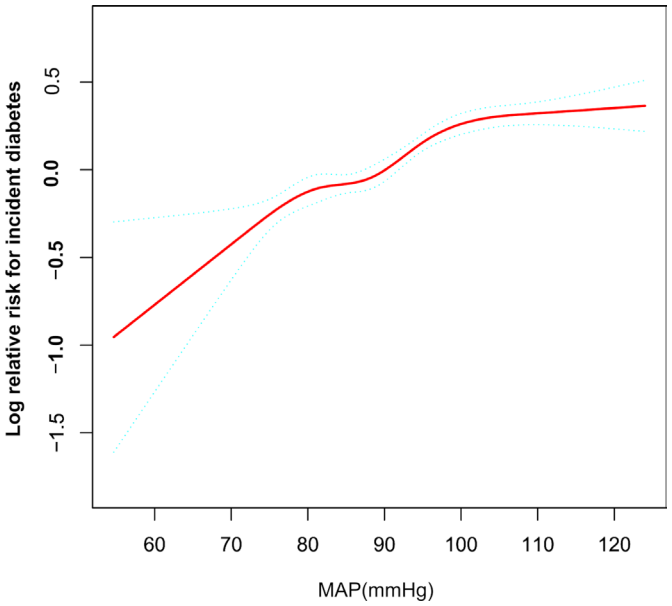

Figure 2 The non-linear relationship between MAP and incident diabetes. A non-linear relationship between MAP and incident diabetes was probed after adjusting for age, gender, BMI, TC, TG, HDL-C, LDL-C, ALT, AST, Scr, family history of diabetes, smoking and drinking status. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratios; LDL-C, low-density lipid cholesterol; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; Scr, serum creatinine; TC, total cholesterol; TG, triglyceride.

0.631) for PP, respectively. The optimal cut-off point of MAP was 92.833 mm Hg, sensitivity was 63.41%, and specificity was 65.93%. As an indicator reflecting the blood pressure status comprehensively, MAP was similar to SBP in predicting diabetes risk. Moreover, MAP was a better predictor of diabetes risk than DBP and PP (figure 3).

DISCUSSION

The present study showed that MAP was an independent predictor for a 5-year risk of incident diabetes after adjusting some covariates. Furthermore, taking MAP equal to the 100.333 mm Hg boundary, this relationship was different on both sides (left (HR:1.022, 95% CI 1.017 to 1.027, p<0.001)); right (HR: 1.005, 95% CI 0.998 to 1.012, p=0.163)). When MAP was below 100.333 mm Hg, the relationship between MAP and incident diabetes is

Table 4 Relationship MAP and the incident diabetes in different models

Variable	Crude model HR, 95% CI, P value	ARD	Model I HR, 95% CI, P value	ARD	Model II HR, 95% CI, P value	ARD
MAP	1.059 (1.057 to 1.062) <0.001	0.09%	1.018 (1.015 to 1.021) <0.001	0.02%	1.008 (1.005 to 1.011) <0.001	0.02%
MAP group						
Low MAP group (MAP <80 mm Hg)	Ref.		Ref.		Ref.	
Medium MAP group (80≤MAP<90 mm Hg)	1.886 (1.646 to 2.162)<0.001	0.53%	1.249 (1.089 to 1.433) 0.002	0.11%	1.070 (0.932 to 1.228) 0.339	0.30%
High MAP group (90≤MAP<100 mm Hg)	3.648 (3.204 to 4.152)<0.001	1.59%	1.580 (1.383 to 1.805)<0.001	0.36%	1.177 (1.029 to 1.345) 0.017	0.57%
Very high MAP group (MAP ≥100 mm Hg)	7.219 (6.354 to 8.203)<0.001	3.62%	1.896 (1.657 to 2.169)<0.001	0.54%	1.265 (1.105 to 1.448) 0.001	0.72%

Crude model: we did not adjust for other covariates.
Model I: we adjust for age, gender, BMI, family history of diabetes, smoking and drinking status.
Model II: we adjust for age, gender, BMI, FPG, TC, TG, HDL-C, LDL-C, ALT, AST, Scr, family history of diabetes, smoking and drinking status.
ALT, alanine aminotransferase; ARD, absolute risk difference; AST, aspartate aminotransferase; BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratios; LDL-C, low-density lipid cholesterol; Ref, reference; Scr, serum creatinine; TC, total cholesterol; TG, triglyceride.

Table 5 The result of two-piecewise linear regression model

	Incident diabetes (HR, 95% CI, P value)
Fitting model by standard linear regression	1.015 (1.012 to 1.018)<0.001
Fitting model by two-piecewise linear regression	
Inflection point of MAP (mm Hg)	100.333
≤100.333	1.022 (1.017 to 1.027)<0.001
>100.333	1.005 (0.998 to 1.012) 0.163
P for log likelihood ratio test	<0.001

We adjusted age, gender, BMI, TC, TG, HDL-C, LDL-C, ALT, AST, Scr, family history of diabetes, smoking and drinking status.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipid cholesterol; MAP, mean arterial pressure; Scr, serum creatinine; TC, total cholesterol; TG, triglyceride.

significant. Subgroup analysis showed a stronger association in the population with age (≥30, <50 years old), FPG <6.1 mmol/L and drinking. Additionally, MAP and SBP have quite similar predictive performance for diabetes (area under the curve (AUC)=0.694 with MAP vs AUC=0.698 with SBP).

Previously, some studies have probed the potential relationship between MAP and incident diabetes. However, most studies were not conducted in the Chinese population.[16 17] In an Iranian study with 701 participants,[16] the researchers found that MAP played the same role in predicting the progression of diabetes as SBP and DBP. The AUC for diabetes was 0.589 for MAP, 0.582 for SBP and 0.658 for DBP. In comparison, the AUCs in our study were larger, 0.694 for MAP, 0.698 for SBP and 0.658 for DBP.[16] The difference may be caused by our study's larger sample size and longer follow-up years. Another study in Cameroon also reached similar conclusions: MAP, SBP and DBP were significantly correlated with diabetes.[16] Contrary to the results of these studies, blood pressure could not predict diabetes risk in a case-referent study among 33 336 participants.[27] A similar study in a Chinese population showed that SBP and DBP were not predictors of incident diabetes.[28] We compared these studies mentioned above, and the inconsistent results may come from the following points: (1) the research population was different and the sample size significantly differed, (2) these findings did not expound the non-linear relationship, (3) these studies did not consider the effect of some important covariates on the relationship between MAP and diabetes. In short, our findings further confirmed that MAP was an independent predictor for diabetes risk in a large Chinese cohort.

Table 6 Effect size of MAP on diabetes in prespecified and exploratory subgroups

Characteristic	Participants	HR (95% CI) P value for interaction
Age (years)		<0.001
20 to <30	28 597	1.000 (0.973 to 1.028) 0.985
30 to <40	82 782	1.021 (1.011 to 1.030)<0.001
40 to <50	45 093	1.012 (1.005 to 1.019) 0.001
50 to <60	29 609	1.006 (1.001 to 1.012) 0.020
60 to <70	17 271	1.001 (0.995 to 1.008) 0.658
≥70	7066	0.999 (0.991 to 1.007) 0.881
Gender		0.085
Male	115 101	1.005 (1.002 to 1.009) 0.003
Female	95 317	1.011 (1.006 to 1.016)<0.001
BMI (kg/m^2)		0.943
<18.5	12 066	0.997 (0.958 to 1.038) 0.892
≥18.5,<24	116 485	1.008 (1.002 to 1.014) 0.005
≥24,<28	64 156	1.009 (1.004 to 1.013)<0.001
≥28	17 711	1.007 (1.001 to 1.014) 0.015
FPG (mmol/L)		<0.001
<6.1	203 401	1.016 (1.012 to 1.020)<0.001
≥6.1	7017	0.999 (0.994 to 1.003) 0.603
HDL-C (mmol/L)		0.242
Low	38 534	1.009 (1.003 to 1.015) 0.003
Medium	37 978	0.999 (0.992 to 1.005) 0.686
High	39 906	1.005 (0.998 to 1.012) 0.204
Not recorded	94 000	1.011 (1.006 to 1.017)<0.001
LDL-C (mmol/L)		0.523
Low	38 867	1.009 (1.002 to 1.016) 0.016
Medium	39 173	1.006 (0.999 to 1.013) 0.082
High	39 504	1.002 (0.996 to 1.008) 0.505
Not recorded	92 874	1.012 (1.006 to 1.017)<0.001
Smoking status		0.188
Current smoker	11 977	1.008 (0.998 to 1.018) 0.138
Ever smoker	2546	1.040 (1.014 to 1.066) 0.002
Never smoker	45 398	1.015 (1.007 to 1.023)<0.001
Not recorded	150 497	1.006 (1.003 to 1.010)<0.001
Drinking status		0.047
Current drinker	1329	1.029 (0.998 to 1.060) 0.063
Ever drinker	8911	1.018 (1.002 to 1.034) 0.025
Never drinker	49 681	1.010 (1.003 to 1.017) 0.003
Not recorded	150 497	1.007 (1.003 to 1.010)<0.001
Family history of diabetes		0.109
No	206 087	1.007 (1.004 to 1.010)<0.001
Yes	4331	1.020 (1.005 to 1.035) 0.010

Continued

Table 6 Continued

Characteristic	Participants	HR (95% CI) P value for interaction

Note 1: Above model adjusted for age, gender, BMI, FPG, TC, TG, HDL-C, LDL-C, ALT, AST, Scr, family history of diabetes, smoking and drinking status.
Note 2: In each case, the model is not adjusted for the stratification variable.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipid cholesterol; Scr, serum creatinine; TC, total cholesterol; TG, triglyceride.

A recent study based on 12 284 participants from rural areas in China's Henan province showed that an increase in MAP could predict the risk of T2DM in women. In our study, the Cox proportional hazard regression model revealed that MAP was positively related to diabetes in women, consistent with that study. However, we found that this relationship also exists in men. The difference may be that our research sample was larger (210 418), and they were from multiple centres, more representative of the Chinese population. Besides, we adjusted different covariates. We adjusted age FPG, ALT, AST and Scr than their research, and they were linked to MAP and diabetes in previous studies.[29–32] In their study, they found a non-linear association between MAP and T2DM. But they did not mention the inflection point. In contrast, we used a two-stage linear regression model to describe the non-linear relationship between MAP and diabetes. We found that the inflection point of MAP was 100.333 mm Hg. When MAP was below 100.333 mm Hg, an increase in MAP caused an increased risk of developing diabetes.

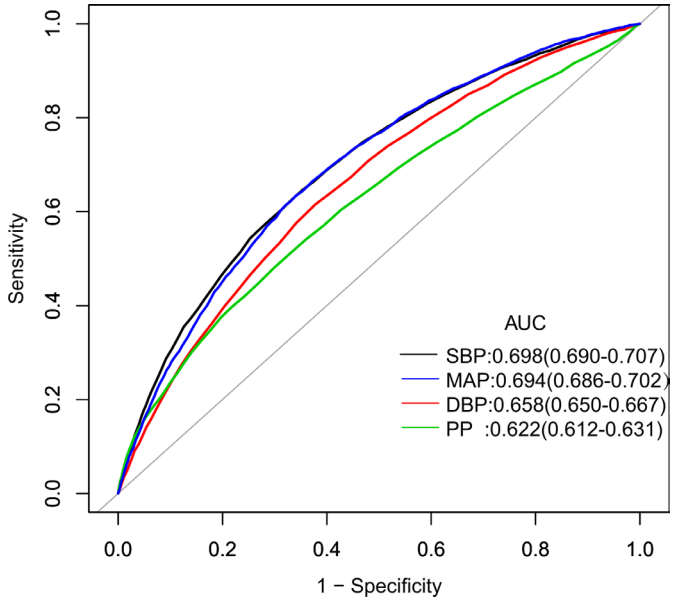

Figure 3 Receiver operating characteristics (ROC) curves with incident diabetes. ROC curves with incident diabetes as the status variable. The areas under the receiver operating characteristics curve (AUCs) were SBP, DBP, MAP and PP. DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

When MAP was more than 100.333 mm Hg, their relationship tended to be saturated. Besides, we found that there was a stronger association in the population with age (≥30,<50 years old), FPG <6.1 mmol/L and drinking, which may be due to the fact that in the population with age (<30 or ≥50 years old), FPG ≥6.1 mmol/L and never drinking, the impact of other risk factors on the incident diabetes exceeds the effects of MAP on diabetes. It is worth mentioning that we analysed the performances and optimal value of the cut-off point of various blood pressure indices. The ROC curve showed that the predictive performance of MAP and SBP was similar in predicting diabetes risk, which was better than DBP and PP. Given that MAP is the average blood pressure throughout a cardiac cycle and a composite blood pressure index that reflects blood pressure status more comprehensively, the effect of MAP on the incident diabetes can better reflect the relationship between blood pressure and diabetes in the real world. Our findings illustrated that people with MAP < 100.333 mm Hg could pay more attention to control MAP to prevent incident diabetes, especially controlling MAP below 92.833 mm Hg. Our findings may be helpful for future research to establish a diagnostic or predictive model of the risk of incident diabetes. And a detailed understanding of MAP as a potential risk factor for incident diabetes will help clinicians provide more personalised prevention and management protocols.

Hypertension and diabetes are often concurrent. Several previous studies showed that hypertension and diabetes have common mediators, including obesity, inflammation, oxidative stress, insulin resistance and endothelial dysfunction.[33–35] So far, researchers have not discovered a direct causal nexus between hypertension and diabetes. Given MAP is a composite blood pressure indicator, elevated MAP is caused by elevated systolic and/or DBP. High blood pressure could lead to endothelial dysfunction, then reduced peripheral vascular flow, which affects insulin delivery and increases insulin resistance.[36–38] It was assumed that oxidative stress induced by hypertension could affect the function of pancreatic β cells, which in turn reduces insulin secretion.[39] Besides, glucose metabolism can be modified by oxidative stress-related cytokines, which may be indirectly related to diabetes.[40] Meanwhile, some researches showed that patients with diabetes and hypertension have low-grade inflammatory reactions.[41–43] Correspondingly, inflammatory markers such as adhesion molecules, cytokines and C reactive protein are increased in these patients.[44] Another study found that about 50% of patients with essential hypertension appear to develop insulin resistance and have an increased risk of diabetes.[45] Thus, insulin resistance could be one of the potential links between blood pressure and diabetes. To our knowledge, high MAP can cause arterial stiffness to progress.[46] However, arterial stiffness could cause impaired microcirculation, and insulin cannot be delivered to target tissues, affecting glucose metabolism and leading to diabetes.[47]

There were some strengths in our study, as follows: (1) our research sample was large and participants were from

multiple centres, more representative of the Chinese population, (2) our study quantitatively assessed the specific relationship between MAP and diabetes, (3) we expounded a non-linear relationship and it was the first study to identify the inflection point of MAP's effect on diabetes, (4) we used rigorous statistical adjustments to reduce confounders' interference with the results, (5) we treated the MAP as a categorical variable, E-value analysis and multiple imputations to do a sensitivity analysis, (6) the subgroup analysis helped us explore other potential risks in the association between MAP and incident diabetes, (7) we used the ROC curves to compare the predictive performance of various blood pressure indices for the risk of diabetes.

There were still some potential limitations. First, the raw data were from the Chinese population; thus, it needs caution to translate and generalise our findings to other races. The generalisability of our findings might be limited. Besides, other related factors were not included in the data, such as glycosylated haemoglobin, medication history, socioeconomic factors, etc. Second, they did not perform a 2-hour oral glucose tolerance test. According to the 1999 WHO diagnostic criteria for diabetes, the definition of diabetes in our study may lead to miss some diabetic patients.[48] However, the 2-hour oral glucose tolerance test was not feasible in such a large cohort. Third, there were some missing values in several variables. However, in order to control bias, we did not exclude missing values for covariates. We mainly supplemented the missing continuous variables with means or median, and others were converted as categorical variables. Besides, we added the multiple imputation method to do sensitivity analysis. Fourth, we only measured MAP and other parameters at baseline, and we did not focus on their changes during follow-up. Fifth, the potential for residual confounding exists in our study, as with all retrospective analysis. However, we adjusted for some confounding factors to the possible influences, and we used the E-value sensitivity analysis to quantify the potential implications of unmeasured confounders and found that unmeasured confounders were unlikely to explain the findings. Sixth, the follow-up duration of this study was 5 years. Once the follow-up time was longer, the relationship between MAP and diabetes may be more significant. Finally, the conclusions were based on retrospective observational design, so prospective studies were needed to further evaluate the relationship between MAP and diabetes.

CONCLUSION

MAP is an independent predictor for 5-year risk of incident diabetes among Chinese adults. The relationship between MAP and incident diabetes is also non-linear. MAP is positively correlated with incident diabetes when MAP is below 100.333 mm Hg. A detailed understanding of MAP as a potential risk factor for incident diabetes will help clinicians provide more personalised prevention and management protocols. This retrospective observational study provides association inference rather than establishing a causal relationship between MAP and diabetes. Therefore, our findings need to be interpreted cautiously and further validated by prospective research.

Contributors YW and HH conceived and designed the research, drafted the manuscript. JC and RC did statistical analysis. XZ and HC took part in the discussion. DY revised the manuscript and acts as the guarantor. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data sharing statementThe raw data can be downloaded from 'DATADRYAD' database (www.Datadryad.org). Dryad Digital Repository. https://datadryad.org/stash/dataset/doi:10.5061/dryad.ft8750v.

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