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# A linear positive association between high-sensitivity C-reactive protein and the prevalence of cardiovascular disease among individuals with diabetes

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## Abstract

**Aims** To assess the correlation between high-sensitivity C-reactive protein (Hs-CRP) and the prevalence of cardiovascular disease (CVD) among individuals with diabetes.

**Methods** A total of 1,555 participants from the National Health and Nutrition Examination Survey were enrolled in this cross-sectional study after excluding individuals without diabetes and those who lacked data on Hs-CRP, diabetes and CVD. All participants were divided into four groups based on quartiles of Hs-CRP: Q1 (≤ 1.20 mg/L), Q2 (1.20–2.86 mg/L), Q3 (2.86–6.40 mg/L), and Q4 (> 6.40 mg/L). Logistic regression analysis, subgroup analysis and restricted cubic spline (RCS) analysis were used to evaluate the correlation between Hs-CRP and the prevalence of CVD in individuals with diabetes.

**Results** In univariate logistic regression analysis, a higher level of Hs-CRP was associated with a higher prevalence of CVD ($P < 0.05$). In the multivariate logistic regression analysis adjusting for confounders, the correlation between Hs-CRP and the prevalence of CVD remained significant (Q3 vs. Q1, OR: 1.505, 95% CI: 1.056–2.147, $P = 0.024$; Q4 vs. Q1, OR: 1.711, 95% CI: 1.171–2.499, $P = 0.006$; $\log_{10}$(Hs-CRP), OR: 1.504, 95% CI: 1.168–1.935, $P = 0.002$). Further subgroup analysis showed that a higher Hs-CRP was independently associated with a higher prevalence of CVD in the < 60 years, male, non-hypertension and non-hypercholesterolemia subgroups ($P < 0.05$). Additionally, RCS analysis revealed a linear positive correlation between Hs-CRP and CVD prevalence (P for nonlinearity = 0.244).

**Conclusion** A higher level of Hs-CRP was closely related to a higher prevalence of CVD in people with diabetes.

**Keywords** High-sensitivity C-reactive protein, Cardiovascular disease, Diabetes, NHANES, Restricted cubic spline

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## Introduction

At present, cardiovascular disease (CVD) and diabetes have become globally recognized as important public health problems and major causes of disability and mortality. Recently, the Global burden of Disease study reported that the global prevalence and mortality of CVD have increased by 93.0% and 53.7%, respectively, over the past 30 years, and the global age-standardized prevalence rate of diabetes has also increased by 90.5%, and the global age-standardized prevalence rate of diabetes is expected to increase by 59.7% between 2021 and 2050, with 1.31 billion people by 2050 living with diabetes [1, 2]. In addition, there has long been a consensus that diabetes is a major causative factor for CVD, and high fasting glucose, insulin resistance and hemoglobin glycation index have also been shown to be major controllable attributing factors for clinical CVD and subclinical CVD [3–5]. Therefore, screening the risk factors of CVD in people with diabetes is very valuable for developing timely and effective prevention strategies.

High-sensitivity C-reactive protein (Hs-CRP) is a marker of inflammation, which not only reflects the state of inflammation, but also has been proved to be involved in the occurrence and development of some metabolic-related diseases and atherosclerosis [6–8]. However, to the best of our knowledge, the correlation between Hs-CRP and the prevalence of CVD in people with diabetes is still unclear. Therefore, to fill this knowledge gap, this study aimed to assess the correlation between Hs-CRP and the prevalence of CVD among individuals with diabetes from the National Health and Nutrition Examination Survey (NHANES).

## Subjects, materials and methods

### Study population

In this large cross-sectional study, all participants were screened from the NHANES (2015–2018). After excluding individuals without diabetes and those who lacked data on Hs-CRP, diabetes and CVD, 1,555 individuals were ultimately included in this study (Fig. 1). The protocol of the study complied with the basic principles of the Declaration of Helsinki and was approved by the National Centers for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board of the United States (#2011-17 and #2018-01). The study participants signed a written informed consent form.

### Data collection and definitions

All data materials for this study were downloaded and integrated from the official NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm), including demographic information, comorbidity and medication information obtained from the household interview questionnaire, and biomarker information. Participants were divided into four groups based on their racial attributes: non-Hispanic White, non-Hispanic Black, Mexican-American and others. Participants were categorised into three groups based on the family poverty income ratio (PIR): ≤ 1.0, 1.0–3.0, and >3.0. Participants were categorised into three groups based on the smoking status: every day, some days, and not at all. Ideal

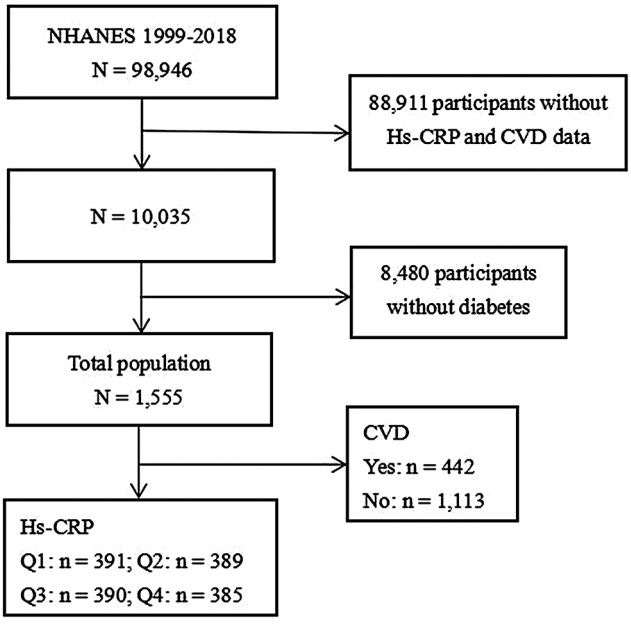


**Fig. 1** Flow chart for study participant. NHANES, National Health and Nutrition Examination Survey; Hs-CRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease

physical activity was defined as participants completing at least 75 min of vigorous-intensity exercise and 150 min of moderate-intensity exercise per week. Diabetes was defined as fasting plasma glucose (FPG)≥7.0 mmol/L, hemoglobin A1c (HbA1c)≥6.5%, or ever having been diagnosed with diabetes by a physician [9]. Hypertension was defined as systolic blood pressure (SBP) or diastolic blood pressure (DBP)≥140 or 90 mmHg, or a previous diagnosis of hypertension by a physician, where the values of SBP and DBP were the average of three non-same-day measurements [10]. Hypercholesterolemia was defined as ever having been diagnosed with hypercholesterolemia by a physician. CVD was defined as ever having been diagnosed by a physician with CVD, including any combination of coronary heart disease, angina pectoris, heart failure, stroke and heart attack. Data on hypotensive drugs and cholesterol-lowering drugs were obtained through the family interview questionnaire. Body mass index (BMI) was measured based on height and weight, that is, BMI=weight (kg) / height ($m^2$).

Blood markers, including triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood urea nitrogen (BUN), creatinine, albumin, uric acid, FPG, HbA1c, and Hs-CRP, were obtained by trained professionals who took blood specimens from participants' veins according to standard procedures and sent them to the standard laboratory for measurement. In this study, serum samples for the determination of Hs-CRP were processed, stored (-30 °C) and shipped to the Collaborative Laboratory Services, Ottumwa, Iowa for analysis by a highly sensitive near-infrared particle immunoassay, that is, the SYNCHRON system automatically proportionally placed the appropriate sample and test dose into a colorimetric dish, then the particles coated with anti-CRP antibody combine with the CRP in the patient sample to form an insoluble aggregate, resulting in turbidity, and then the change in absorbance is proportional to the concentration of Hs-CRP in the sample. Finally, the concentration of Hs-CRP is calculated according to the pre-determined single point adjustment calibration curve and expressed in units of mg/L. In this study, all participants were divided into four groups based on quartiles of Hs-CRP: Q1 (≤1.20 mg/L), Q2 (1.20–2.86 mg/L), Q3 (2.86–6.40 mg/L), and Q4 (>6.40 mg/L).

### Statistical analysis

Categorical variables were expressed as number of cases (percentage), and comparisons between groups were made using the chi-square test or Fisher's exact test. Normally distributed continuous variables were expressed as mean±standard deviation, and one-way ANOVA was used for comparisons between groups. Non-normally distributed continuous variables were expressed as median (quartiles), and comparisons between groups were performed using nonparametric tests (Kruskal-Wallis H test). Since Hs-CRP did not fit a normal distribution, $\log_{10}$(Hs-CRP) was used to fit the regression analysis. In addition, Hs-CRP was standardised to better explain the effect of prevalence of CVD with changes in Hs-CRP. Then univariate logistic regression analysis was used to test the association of each variable with the prevalence of CVD in individuals with diabetes, and then variables with $P<0.05$ were selected for inclusion in multivariate logistic regression analysis. In multivariate logistic regression analysis, four models were constructed for testing the correlation between Hs-CRP and the prevalence of CVD. Model 1 was not adjusted for any covariates; model 2 was adjusted for age and sex only; model 3 was adjusted for age, sex, race, hypertension, hypotensive drugs, hypercholesterolemia and cholesterol-lowering drugs; model 4 was adjusted for age, sex, race, hypertension, hypotensive drugs, hypercholesterolemia, cholesterol-lowering drugs, SBP, DBP, total cholesterol, LDL-C, HDL-C, BUN, creatinine, albumin, uric acid, and HbA1c. All participants were then divided into eight subgroups based on the four variables of age, sex, hypertension, and hypercholesterolemia to verify the stratified correlation between Hs-CRP and CVD prevalence, respectively. Finally, restricted cubic spline (RCS) plot was used to explore the nonlinear correlation between Hs-CRP and CVD prevalence. All statistical analyses were performed using SPSS 26.0 and R 4.1.3, and $P<0.05$ was identified as a statistically significant difference.

## Results

### Baseline characteristics

As shown in Table 1. There were significant differences in age, sex, race, family PIR, smoking status, CVD, cholesterol-lowering drugs, BMI, triglyceride, total cholesterol, LDL-C, HDL-C, albumin, uric acid, FPG, and HbA1c among the four groups of Hs-CRP, with the prevalence of CVD increasing with Hs-CRP levels ($P<0.05$).

### Association between Hs-CRP and CVD

Table 2 presented the results of logistic regression analysis of the association between Hs-CRP and CVD. In univariate logistic regression analysis, a higher level of Hs-CRP was associated with a higher prevalence of CVD ($P<0.05$). After adjusting for age, sex, race, hypertension, hypotensive drugs, hypercholesterolemia, cholesterol-lowering drugs, SBP, DBP, total cholesterol, LDL-C, HDL-C, BUN, creatinine, albumin, uric acid and HbA1c, a higher level of Hs-CRP was still strongly associated with a higher prevalence of CVD (Q3 vs. Q1, OR: 1.505, 95% CI: 1.056–2.147, $P=0.024$; Q4 vs. Q1, OR: 1.711, 95% CI: 1.171–2.499, $P=0.006$; $\log_{10}$(Hs-CRP), OR: 1.504, 95% CI: 1.168–1.935, $P=0.002$).

**Table 1** Baseline characteristics of participants stratified by the Hs-CRP

| | Total population | Q1 | Q2 | Q3 | Q4 | *P* value |
|---|---|---|---|---|---|---|
| N | 1,555 | 391 | 389 | 390 | 385 | |
| Age, years | 62.16 ± 12.84 | 64.85 ± 12.40 | 63.29 ± 12.57 | 61.12 ± 12.74 | 59.35 ± 13.00 | < 0.001 |
| Sex, male, n (%) | 852 (54.80%) | 248 (63.40%) | 228 (58.60%) | 214 (54.90%) | 162 (42.10%) | < 0.001 |
| Race, n (%) | | | | | | < 0.001 |
| Non-Hispanic White | 470 (30.20%) | 97 (24.80%) | 130 (33.40%) | 122 (31.30%) | 121 (31.40%) | |
| Non-Hispanic Black | 351 (22.60%) | 74 (18.90%) | 78 (20.10%) | 89 (22.80%) | 110 (28.60%) | |
| Mexican-American | 308 (19.80%) | 81 (20.70%) | 81 (20.80%) | 76 (19.50%) | 70 (18.20%) | |
| Others | 426 (27.40%) | 139 (35.50%) | 100 (25.70%) | 103 (26.40%) | 84 (21.80%) | |
| Family PIR, n (%) | | | | | | 0.013 |
| ≤ 1.0 | 335 (24.40%) | 76 (22.30%) | 71 (20.30%) | 98 (28.70%) | 90 (26.40%) | |
| 1.0–3.0 | 622 (45.30%) | 150 (44.00%) | 155 (44.40%) | 150 (43.90%) | 167 (49.00%) | |
| > 3.0 | 416 (30.30%) | 115 (33.70%) | 123 (35.20%) | 94 (27.50%) | 84 (24.60%) | |
| Smoking status, n (%) | | | | | | 0.020 |
| Every day | 180 (19.00%) | 36 (14.60%) | 36 (15.90%) | 49 (21.50%) | 59 (23.90%) | |
| Some days | 45 (4.70%) | 13 (5.30%) | 7 (3.10%) | 8 (3.50%) | 17 (6.90%) | |
| Not at all | 724 (76.30%) | 198 (80.20%) | 184 (81.10%) | 171 (75.00%) | 171 (69.20%) | |
| Ideal physical activity, n (%) | 328 (21.10%) | 91 (23.30%) | 82 (21.10%) | 89 (22.80%) | 66 (17.10%) | 0.143 |
| Comorbidities, n (%) | | | | | | |
| Hypertension | 1076 (69.40%) | 254 (65.10%) | 276 (71.30%) | 263 (67.80%) | 283 (73.50%) | 0.056 |
| Hypercholesterolemia | 935 (61.40%) | 223 (58.80%) | 248 (64.60%) | 248 (64.60%) | 216 (57.40%) | 0.078 |
| Cardiovascular disease | 442 (28.40%) | 91 (23.30%) | 113 (29.00%) | 115 (29.50%) | 123 (31.90%) | 0.048 |
| Medication, n (%) | | | | | | |
| Hypotensive drugs | 952 (63.00%) | 226 (59.60%) | 238 (63.60%) | 238 (62.60%) | 250 (66.00%) | 0.340 |
| Cholesterol-lowering drugs | 822 (57.20%) | 222 (61.70%) | 230 (63.00%) | 196 (54.90%) | 174 (49.00%) | < 0.001 |
| Body mass index, kg/m$^2$ | 32.53 ± 7.77 | 28.25 ± 5.24 | 31.20 ± 5.87 | 33.66 ± 6.98 | 37.15 ± 9.50 | < 0.001 |
| Systolic blood pressure, mmHg | 133.06 ± 20.31 | 134.85 ± 22.36 | 133.34 ± 19.38 | 132.59 ± 18.70 | 131.49 ± 20.59 | 0.147 |
| Diastolic blood pressure, mmHg | 69.76 ± 12.23 | 69.66 ± 11.76 | 69.43 ± 11.96 | 70.61 ± 12.19 | 69.33 ± 12.96 | 0.461 |
| Triglyceride, mmol/L | 1.32 (0.93, 1.87) | 1.14 (0.73, 1.67) | 1.25 (0.90, 1.83) | 1.42 (1.02, 1.90) | 1.44 (1.02, 2.11) | < 0.001 |
| Total cholesterol, mmol/L | 4.56 ± 1.16 | 4.30 ± 1.03 | 4.54 ± 1.18 | 4.71 ± 1.26 | 4.69 ± 1.10 | < 0.001 |
| LDL-C, mmol/L | 2.55 ± 0.98 | 2.25 ± 0.85 | 2.54 ± 0.97 | 2.66 ± 1.10 | 2.80 ± 0.92 | < 0.001 |
| HDL-C, mmol/L | 1.25 ± 0.38 | 1.36 ± 0.42 | 1.24 ± 0.37 | 1.22 ± 0.37 | 1.19 ± 0.36 | < 0.001 |
| Blood urea nitrogen, mmol/L | 6.43 ± 3.12 | 6.43 ± 2.63 | 6.32 ± 2.52 | 6.25 ± 3.30 | 6.72 ± 3.86 | 0.162 |
| Creatinine, umol/L | 91.23 ± 69.01 | 89.80 ± 63.44 | 84.44 ± 38.95 | 93.29 ± 79.42 | 97.48 ± 84.75 | 0.059 |
| Albumin, g/L | 40.66 ± 3.79 | 42.22 ± 3.26 | 41.57 ± 3.28 | 40.45 ± 3.67 | 38.36 ± 3.75 | < 0.001 |
| Uric acid, umol/L | 338.05 ± 94.33 | 323.85 ± 84.82 | 330.99 ± 81.30 | 344.11 ± 101.57 | 353.52 ± 105.13 | < 0.001 |
| Fasting plasma glucose, mmol/L | 9.02 ± 3.67 | 8.24 ± 2.62 | 9.00 ± 3.63 | 9.43 ± 4.11 | 9.48 ± 4.10 | 0.002 |
| Hemoglobin A1c, % | 7.48 ± 1.77 | 7.18 ± 1.47 | 7.32 ± 1.69 | 7.77 ± 1.94 | 7.65 ± 1.88 | < 0.001 |

Hs-CRP, high-sensitivity C-reactive protein; PIR, poverty income ratio; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

### Subgroup analysis and RCS analysis

As shown in Table 3. Further subgroup analysis showed that a higher Hs-CRP was independently associated with a higher prevalence of CVD in the <60 years, male, non-hypertension and non-hypercholesterolemia subgroups (Q4 vs. Q1, OR: 4.094, 95% CI: 1.615–10.380, $P<0.01$; Q4 vs. Q1, OR: 1.962, 95% CI: 1.151–3.342, $P<0.05$; Q4 vs. Q1, OR: 6.426, 95% CI: 2.760-14.961, $P<0.001$; Q4 vs. Q1, OR: 2.344, 95% CI: 1.192–4.609, $P<0.05$). Additionally, RCS analysis revealed a linear positive correlation between Hs-CRP and CVD prevalence (P for nonlinearity = 0.244) (Fig. 2).

## Discussion

In this population-based cross-sectional study, we confirmed for the first time a linear positive correlation between Hs-CRP and the prevalence of CVD in people with diabetes, and further found a stratified correlation between Hs-CRP and CVD prevalence in the less than 60 years, male, non-hypertension or non-hypercholesterolemia population, which warrants further discussion on the importance of Hs-CRP in the occurrence and development of CVD.

In recent years, the correlation between inflammation and CVD has been increasingly reported. For example, new inflammatory markers representing systemic inflammation have been shown to be closely related not only to

**Table 2** Association of Hs-CRP with cardiovascular disease

| | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | *P* value | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| Q1 | Ref | - | Ref | - | Ref | - | Ref | - |
| Q2 | 1.350 (0.979, 1.860) | 0.067 | 1.549 (1.108, 2.166) | 0.011 | 1.393 (0.986, 1.967) | 0.060 | 1.332 (0.941, 1.887) | 0.106 |
| Q3 | 1.379 (1.001, 1.899) | 0.049 | 1.816 (1.295, 2.547) | 0.001 | 1.713 (1.210, 2.423) | 0.002 | 1.505 (1.056, 2.147) | 0.024 |
| Q4 | 1.548 (1.126, 2.126) | 0.007 | 2.414 (1.711, 3.407) | < 0.001 | 2.223 (1.557, 3.174) | < 0.001 | 1.711 (1.171, 2.499) | 0.006 |
| P for trend | - | 0.053 | - | < 0.001 | - | < 0.001 | - | 0.038 |
| Hs-CRP[a] | 1.012 (1.003, 1.020) | 0.006 | 1.016 (1.007, 1.026) | < 0.001 | 1.015 (1.006, 1.024) | 0.001 | 1.007 (0.997, 1.016) | 0.155 |
| Hs-CRP[b] | 1.157 (1.042, 1.284) | 0.006 | 1.228 (1.096, 1.377) | < 0.001 | 1.210 (1.080, 1.355) | 0.001 | 1.089 (0.968, 1.225) | 0.155 |
| $Log_{10}$(Hs-CRP) | 1.391 (1.135, 1.703) | 0.001 | 1.827 (1.464, 2.280) | < 0.001 | 1.769 (1.406, 2.225) | < 0.001 | 1.504 (1.168, 1.935) | 0.002 |

[a] The OR was examined by per 1-unit increase of Hs-CRP; [b] The OR was examined by per 1-SD increase of Hs-CRP. Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for variables included in Model 2 and race, hypertension, hypotensive drugs, hypercholesterolemia and cholesterol-lowering drugs; Model 4: adjusted for variables included in Model 3 and systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood urea nitrogen, creatinine, albumin, uric acid and hemoglobin A1c. Hs-CRP, high-sensitivity C-reactive protein; OR, odd ratio; CI, confidence interval

**Table 3** Stratified correlation between Hs-CRP and cardiovascular disease

| | Q1 | Q2 | Q3 | Q4 | | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | P for trend | P for interaction |
| Age | | | | | | 0.568 |
| < 60 years | Ref | 2.272 (0.815, 6.337) | 3.635 (1.408, 9.385)** | 4.094 (1.615, 10.380)** | 0.016 | |
| ≥ 60 years | Ref | 1.324 (0.900, 1.946) | 1.301 (0.861, 1.967) | 1.447 (0.926, 2.260) | 0.364 | |
| Sex | | | | | | 0.001 |
| Male | Ref | 1.503 (0.955, 2.365) | 1.787 (1.115, 2.864)* | 1.962 (1.151, 3.342)* | 0.050 | |
| Female | Ref | 1.136 (0.629, 2.051) | 1.285 (0.700, 2.360) | 1.345 (0.729, 2.482) | 0.794 | |
| Hypertension | | | | | | 0.089 |
| Yes | Ref | 1.130 (0.759, 1.683) | 1.391 (0.920, 2.103) | 1.236 (0.797, 1.917) | 0.467 | |
| No | Ref | 2.574 (1.166, 5.678)* | 2.151 (0.942, 4.911) | 6.426 (2.760, 14.961)*** | < 0.001 | |
| Hypercholesterolemia | | | | | | 0.407 |
| Yes | Ref | 1.191 (0.763, 1.860) | 1.594 (1.000, 2.542) | 1.393 (0.835, 2.324) | 0.253 | |
| No | Ref | 1.666 (0.892, 3.113) | 1.473 (0.756, 2.868) | 2.344 (1.192, 4.609)* | 0.095 | |

The multivariate adjusted model used in the subgroups analysis consisted of all covariates used in model 4 in Table 2 except for the variable that was used for stratification. The interaction of Hs-CRP and variables used for stratification was examined by likelihood ratio tests. *$p<0.05$, **$p<0.01$, ***$p<0.001$. Hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index; OR, odd ratio; CI, confidence interval

CVD in diabetic patients but also to the mortality of CVD [11, 12]. Besides, current evidence suggests that Hs-CRP is also associated with CVD and a number of metabolic-related diseases. For example, a systematic review and meta-analysis including 12 case-control studies and 8,345 patients showed that Hs-CRP could predict the risk of abdominal aortic aneurysms of intermediate or small aortic diameter [13]. In addition, Liu et al. revealed an independent association of Hs-CRP with all-cause death, cardiac death, and major adverse cardiovascular and cerebrovascular events in a study involving 3,069 elderly patients with coronary artery disease with three-vessel disease [14]. Furthermore, in a cross-sectional study including only patients with type 2 diabetes, Tang et al. found that patients with Hs-CRP levels in the fourth quartile had a 96.8% increased risk of diabetic nephropathy compared to patients with Hs-CRP levels in the first quartile, and both in the total population and in a sex-specific population, the RCS further revealed a a linear positive association between Hs-CRP and risk of diabetic nephropathy [15]. In another real-world study that included only 1,804 patients with acute myocardial infarction, Hs-CRP was not only shown to be an independent predictor of in-hospital poor prognosis, but was also shown to improve the predictive power of the GRACE score for in-hospital poor prognosis [16]. Moreover, in a prospective cohort study including 4.8 years of follow-up and 1,281 patients with acute heart failure, long-term cumulative exposure to higher levels of Hs-CRP also had a significant impact on poor prognosis and mortality in hospitalised patients with heart failure, suggesting that long-term monitoring of Hs-CRP is of great interest for the prevention of cardiovascular events [17]. Additionally, in a community-based prospective cohort study, Yoshikawa et al. found that after 24 years of follow-up, participants in the third and fourth quartiles of Hs-CRP levels had 1.77 and 1.89 times the risk of developing atrial fibrillation compared with those in the first quartile of Hs-CRP levels, respectively [18]. Furthermore, another community-based cohort study from China

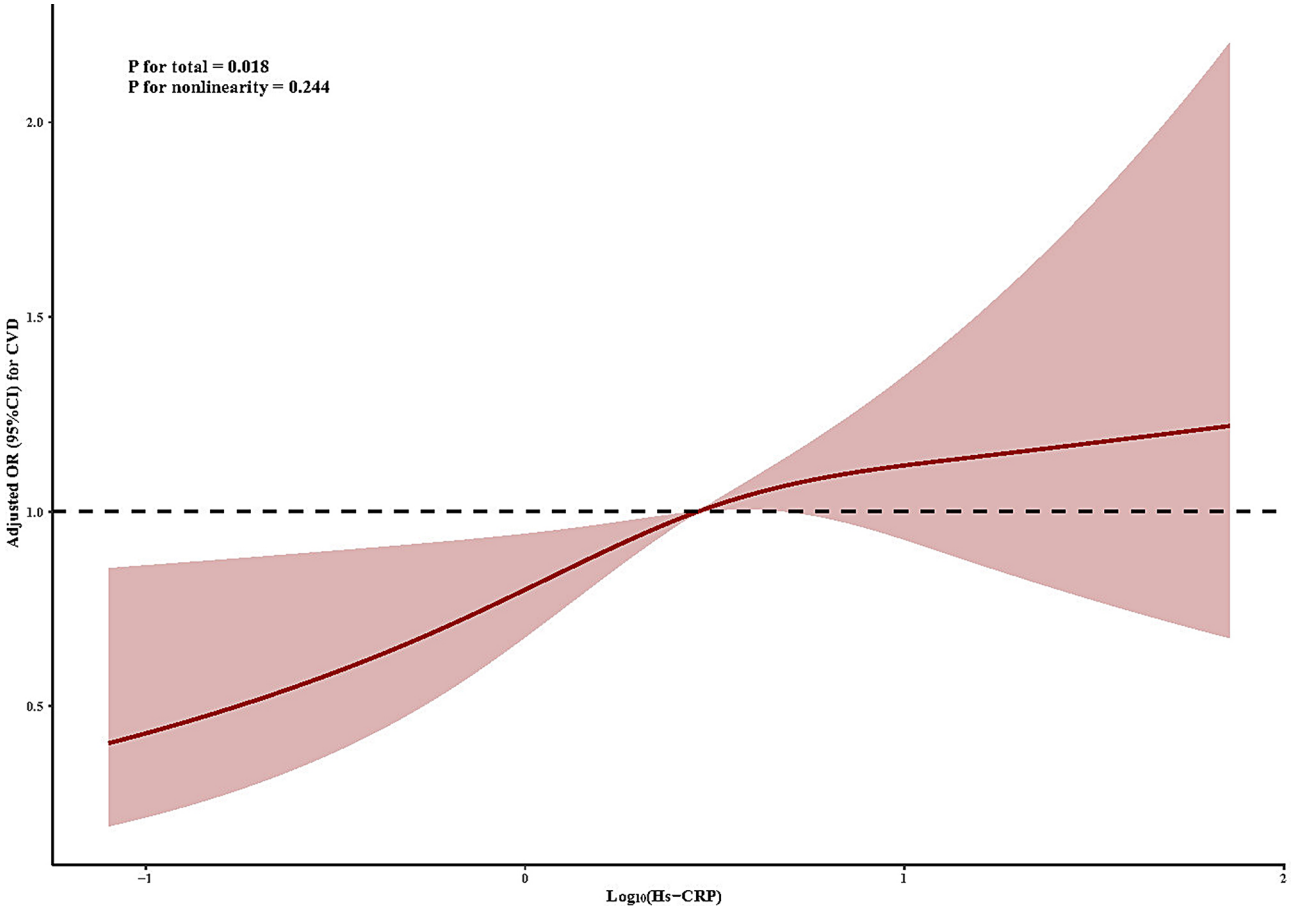


**Fig. 2** RCS plot for evaluating the nonlinearity of Hs-CRP and cardiovascular disease. Hs-CRP, high-sensitivity C-reactive protein; OR, odd ratio; CI, confidence interval

demonstrated a 64%, 25%, and 31% increased risk of atrioventricular block, left bundle branch block, and right bundle branch block, respectively, in individuals with Hs-CRP > 3 mg/L compared to individuals with Hs-CRP ≤ 3 mg/L, and the RCS further showed a linear positive correlation between Hs-CRP and the risk of atrioventricular block, left bundle branch block and right bundle branch block, suggesting that lowering high levels of Hs-CRP is also essential for preventing the risk of heart block [19]. In addition, Lee et al. found that higher levels of Hs-CRP were strongly associated with a higher risk of all-cause mortality, cancer mortality, and CVD mortality in the general population after a 6.8-year follow-up of 41,070 men and 81,011 women [20]. For CVD, Kuppa et al. have confirmed the causal relationship between CRP and the risk of CVD in the Mendelian randomization study, but the causal relationship between Hs-CRP and the risk of CVD is still unknown [21]. Nevertheless, several observational studies have consistently shown a close correlation between Hs-CRP and CVD. For example, Dong et al. found in a large prospective cohort study that included 8,688 CVD-free middle-aged adults and a median follow-up time of 6.34 years that individuals in the third tertile of Hs-CRP had a 1.62-fold higher risk of CVD than those in the first tertile, but they did not confirm a correlation between changes in Hs-CRP during follow-up and the incidence of CVD [22]. In addition, although Koosha et al. confirmed the association of Hs-CRP with the prevalence of CVD in the total population in the Isfahan Cohort Study, the association of Hs-CRP with the prevalence of CVD in the diabetic population was not determined in multivariate logistic regression model adjusted only for age and sex [23]. Additionally, in a community-based cohort study that included 53,065 participants with three Hs-CRP measurements over a 6-year period, Wang et al. found that individuals with all three measurements of Hs-CRP ≥ 3 mg/L had a 38% increased risk of CVD compared with individuals with all three measurements of Hs-CRP < 3 mg/L, and that the risk of CVD increased by 4% for every 1 mg/L increase in baseline Hs-CRP and by 17% for every 1 mg/L increase in the mean of the three measurements of Hs-CRP [24]. For the diabetic population, several studies have also found that Hs-CRP has a certain

predictive value for CVD among diabetes. For instance, Aryan and colleagues followed up with 1,301 diabetic patients and found that baseline Hs-CRP levels could predict both coronary heart disease and microvascular complications in diabetic patients [25]. Additionally, Hsieh and others have indicated that Hs-CRP may help in detecting asymptomatic myocardial ischemia in diabetic patients, thereby reducing future incidence and mortality rates of CVD [26]. Furthermore, Zhou and colleagues also discovered that Hs-CRP can accurately detect the characteristics of coronary artery narrowing and plaque in diabetic patients, having significant clinical value in the risk assessment of CVD [27]. However, these studies did not further explore the association between Hs-CRP and CVD prevalence among individuals with diabetes. Based on this research background, we assessed the association between multiple Hs-CRP metrics and CVD prevalence among individuals with diabetes in this community-based cohort study, and found that individuals in the third and fourth quartiles of Hs-CRP levels had a 50.5% and 71.1% increased prevalence of CVD, respectively, compared with individuals in the first quartile of Hs-CRP levels, and for each unit increase in log10 (Hs-CRP), a 50.4% increase in CVD prevalence. In addition, we also found that the CVD prevalence of Q4 patients under 60 years old, male, without hypertension and without hypercholesterolemia was 4.09, 1.96, 6.43 and 2.34 times higher than that of Q1 patients, respectively. In addition, our study showed that Hs-CRP levels vary significantly among different ethnic groups and sexes. Therefore, when forming the quartile groups for regression analysis, we adjusted for gender and ethnicity to account for these differences. This helps to ensure that our results are more accurate and representative. More importantly, we also confirmed a linear positive correlation between Hs-CRP and CVD prevalence in RCS analysis. Furthermore, in Model 1, we used Hs-CRP as a continuous variable, which allows us to capture the subtle variations in Hs-CRP levels and their association with the prevalence of CVD. Continuous variable analysis typically has higher statistical power because it utilizes the information from all data points. However, when we divided the Hs-CRP data into four groups for quartile analysis, although this method simplifies analysis and interpretation, it can also lead to information loss. For example, the variability of Hs-CRP levels within groups might be overlooked, reducing the ability to detect small but significant associations. Therefore, in Model 1, the quartiles were not associated with the presence of prevalent CVD. In the adjusted models, we controlled for other potential confounding variables such as age, sex, and ethnicity, which helps to eliminate their impact on the association between Hs-CRP and CVD. The adjusted models better reflect the true relationship between Hs-CRP and CVD, resulting in significant associations between Hs-CRP quartiles and the outcome in the adjusted models. To further verify this phenomenon, we conducted sensitivity analyses using both continuous variables and categorical variables (quartiles). The results showed that the adjusted models demonstrated a significant association between Hs-CRP and CVD regardless of the variable type. This supports our hypothesis that the association between Hs-CRP and CVD becomes more pronounced after adjusting for confounding variables. In summary, continuous variable analysis can utilize more information and has higher statistical power, while categorical variable analysis is easier to interpret but may lose some information. These steps help us ensure the stability of the regression models and the reliability of the results.

In addition, further discussion is still needed on the potential mechanisms underlying the association of Hs-CRP with CVD. At the clinical phenotype level, there is an inextricable correlation between Hs-CRP and hypertension, diabetes, chronic kidney disease, metabolic syndrome, and cardiac arrhythmias [28–32], and thus Hs-CRP may indirectly increase the risk of CVD through these diseases. At the molecular and cellular level, Hs-CRP as a major inflammatory marker may promote mechanisms such as inflammatory stress and oxidative stress, which in turn lead to thrombosis, vascular calcification and atherosclerosis, ultimately contributing to the development of CVD [33–36]. These potential mechanisms are now widely recognised, but more basic and clinical studies are needed to continue to uncover more mechanisms.

Although the study had meaningful results, there were still several limitations. First, NHANES is a national sample survey in the United States, but we did not take into account the adjustment of weights when analyzing the data, so the results of this study did not represent the real situation of the American population, but could only reflect the health and nutritional status of these participants. Second, due to the cross-sectional nature of this study, we could not determine the causal link between Hs-CRP and CVD prevalence. Besides, one limitation of this study was the lack of a sample size analysis. This was primarily due to the nature and data source of our study. This study was observational, aiming to explore the relationship between Hs-CRP levels and the prevalence of CVD in the diabetic population. Observational studies primarily analyze existing data rather than conducting interventions with predefined control groups, hence there is no necessity for a sample size analysis. And the data used in this study was sourced from NHANES, a national cross-sectional survey with a predetermined sample size and distribution. Therefore, we used the existing sample data for analysis rather than conducting a sample size analysis through additional data collection

or intervention. Nevertheless, we adhered strictly to statistical principles during the data analysis process and provided detailed explanations and discussions of the subgroup analysis results to ensure the scientific validity and reliability of the study findings. Although we did not conduct a sample size analysis, this did not affect the main conclusions of our research. Third, this study did not include data from other countries and regions, so the promotion of the study results was limited. Fourth, we did not test the correlation between Hs-CRP and CVD prevalence in non-diabetic people, so it is unknown whether diabetes status affects major outcomes. Fifth, since the CVD in this study was defined by an arbitrary combination of several diseases, it is impossible to know whether Hs-CRP can predict a single CVD component. Sixth, CRP, which is also a marker of inflammation like Hs-CRP, has also been confirmed to be involved in the occurrence and development of atherosclerosis, but due to the lack of CRP indicators in these data, we have not been able to explore the correlation between CRP and the prevalence of CVD in people with diabetes. Seventh, another limitation of this study was the lack of data on the duration of diabetes. We could not assess the potential impact of disease duration on the association between Hs-CRP and CVD. Additionally, we did not have detailed data to analyze the differences in the association between Hs-CRP and CVD in screen-detected diabetes versus physician-diagnosed diabetes. Finally, this study lacked specific data on the use of major drug categories. Although certain drugs are known to reduce Hs-CRP levels, we did not have data on their use, making it impossible to assess the potential impact of these drugs on our research findings. This limitation may restrict our comprehensive understanding of the relationship between Hs-CRP levels and the prevalence of CVD.

## Conclusions

In this cross-sectional study based on a community-based diabetic population, we not only confirmed the association between Hs-CRP and CVD prevalence, but also found an independent correlation between Hs-CRP and CVD in the less than 60 years population, males, non-hypertension population, and non-hypercholesterolemia population, and further revealed a linear positive correlation between them. These data suggest that the inclusion of Hs-CRP in routine screening for diabetes may help identify high-risk individuals and assist in managing CVD.

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**Author contributions**
Yu Liu: Data curation, Writing - original draft. Yu Liu: Conceptualization, Methodology, Software. Yu Liu, Wei He, Yuan Ji, Qingjie Wang and Xun Li: Writing - review & editing. Xun Li: Conceptualization, Funding acquisition, Project administration, Supervision. All authors read and approved the final manuscript.

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**Data availability**
The data and information contained in this study are available on a publicly available website. (https://www.cdc.gov/nchs/nhanes/index.htm).

## Declarations

**Ethics approval and consent to participate**
The protocol complied with the basic principles of the Declaration of Helsinki and was approved by the National Centers for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board of the United States. The study participants signed a written informed consent form.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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