

Nonlinear Relationship Between HbA1c and Coronary Artery Calcium Score Progression: A Secondary Analysis Based on a Retrospective Cohort Study

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Research

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Abstract

Objective

Some previous studies was to clarify the correlation between glycated hemoglobin(HbA1c) and coronary heart disease (CHD) and the evidence regarding the correlation was still debated. However, there are fewer scientific dissertations about the correlation between HbA1c and coronary artery calcium score progression. Consequently, the present study was undertaken to explore the link of HbA1c on coronary artery calcium score progression in South Korea.

Methods

This study is a secondary analysis based on a retrospective cohort study. 8151 participants received a health check-up program at the Health Promotion Center of the Samsung Medical Center in Seoul, South Korea, from March 1, 2003 to December 31, 2013. We then used Cox proportional-hazards regression model to evaluate the independent relationship between HbA1c and coronary artery calcium score progression.

Results

After adjusting potential confounders (age, sex, BMI, height, weight, SBP, DBP, TC, LDL-C, HDL-C, triglycerides, smoking status, alcohol consumption, reflux esophagitis status, hypertension, diabetes, dyslipidemia, ischemic heart disease and cerebrovascular disease), non-linear relationship was detected between HbA1c and coronary artery calcium score progression, whose point was 5.8%. The effect sizes and the confidence intervals on the left and right sides of inflection point were 2.05 (1.85 to 2.27) and 1.04 (0.99 to 1.10) , respectively.

Conclusion

The relationship between HbA1c and coronary artery calcium score progression is non-linear. HbA1c is positively related with coronary artery calcium score progression when HbA1c was less than 5.8%.

Introduction

Glycated hemoglobin (HbA1c) is the core of glycemic control and management in diabetic patients, and has recently been recommended for diagnosing diabetes and identifying people at risk of developing diabetes[1]. Compared with fasting or post-load blood glucose measurement, HbA1c has better reliability[2]. HbA1c can effectively reflect blood glucose control in the past 2–3 months, and is a diagnosis and recommendation for diabetes screening tool[3–4].

Coronary atherosclerotic heart disease (coronary heart disease for short, CHD) is a multi-cause disease. The Framingham Heart Study in the United States has identified a series of risk factors for coronary heart disease, including age, gender, cholesterol, hypertension, smoking and diabetes[5]. It is well known that

chronic glucose metabolism disorders increase the risk of CHD[6–9]. However, many previous studies regarding the association between HbA1c and CHD yielded conflicting findings. Many studies reported that HbA1c was an important determinant of CHD and its severity[10–14]. However, Other researches suggested that the association between HbA1c and CHD was not significant[15], and it was controversial whether it was necessary to control the patient's HbA1c below 7% or even close to the normal level[16]. In view of the differences in study population, study design, measurement (define) of coronary artery stiffness, adjustment for covariates, and certain methodological limitations, we conducted a secondary analysis based on a retrospective cohort study to observe the correlation between HbA1c and the progression of coronary artery calcium scores in people undergoing physical examinations at the Health Promotion Center.

Participants And Methods

Study design

This research is a retrospective cohort study design. The interesting independent variable in the present work is HbA1c. The dependent variable is coronary artery calcium score progression (dichotomous variable : 0 = no progression, 1 = progression).

Data source

We obtained data from the "PLOS ONE" database (<https://journals.plos.org/plosone/>). This website allowed users to download raw data for free. According to PLOS ONE Terms of Service, we cited PLOS ONE data package in the present study. (PLOS ONE data package: Min YW, Song BG, Kim HS, Kim K, Lee H, Min BH, Lee JH, Son HJ, Rhee PL, Kim JJ (2017) Data from: Associations between reflux esophagitis and the progression of coronary artery calcification: A cohort study.

<https://doi.org/10.1371/journal.pone.0184996.s001>).

Study population

Yang Won Min et al.[17] completed the entire study. In order to allow to understand the entire research process more clearly, we have outlined the steps of the study here. The specific details are described in the original, reported by Yang Won Min et al. They non-selectively and consecutively collected persons who had undergone physical examinations at the Health Promotion Center of the Samsung Medical Center in Seoul, South Korea, from March 1, 2003 to December 31, 2013. To ensure the privacy of participants, Yang Won Min et al. encoded their identity information as the non-traceable codes. Clinical data were extracted from hospital electronic medical record system.

Initially, 199375 participants were initially involved in this study; 191224 participants were subsequently excluded from this study, leaving 8151 cases for the final data analysis (see flowchart for details, Fig. 1). Inclusion criteria included: (1) Participants were aged over 20 years and underwent health screening examinations;(2) Participants underwent screening esophagogastroduodenoscopy (EGD) and coronary computed tomography (CT) scanning during the same visit. Participants who did not undergo follow-up

coronary CT scans (n = 19,038) and had missing information (n = 89) were excluded. We also excluded participants who were missing HbA1c at the first physical examination (n = 70). The author has detailed ethics and informed consent in previously published articles[17].

Variables

HbA1c

The information of HbA1c were obtained at baseline and were recorded as continuous variable.

Coronary artery calcium score progression

Our interesting outcome variable was coronary artery calcium score progression (dichotomous variable : 0 = no progression, 1 = progression). Brilliance 40 (Philips Medical Systems, Cleveland, Ohio), VCT LightSpeed 64 (GE Healthcare, Milwaukee, Wisconsin), or Discovery 750HD (GE Healthcare) multidetector CT scanners were used to acquire images of CAC. The scans were analyzed using Extended Brilliance Workspace (Philips Medical Systems) or Advantage (GE Healthcare) workstations. The CAC scores were calculated as described by Agatston et al. [18].

Covariates

In this study, the selection of covariates was based on published literature and our clinical experience. Based on the above principles, the following variables were used as covariates : (1) continuous variables: age, duration, body mass index (BMI), height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), diastolic blood pressure (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides; (2) categorical variables: sex (male, female), smoking status (never, past smoker, current smoker), alcohol consumption (never, past drinker, current drinker), reflux esophagitis status (negative, positive), hypertension (negative, positive), diabetes (negative, positive), dyslipidemia (negative, positive), ischemic heart disease (negative, positive), cerebrovascular disease (negative, positive).

Statistical analysis

Data are indicated as mean \pm standard deviation (normal distribution) or median (min,max)(skewed distribution) for continuous variables and as numbers and percentages for categorical variables. χ^2 (categorical variables), student T test (normal distribution), or Man Whitney U test (skewed distribution) were used to detect the differences among different coronary artery calcium score progression (binary variable). To examine the association between HbA1c and coronary artery calcium score progression, we constructed three distinct models using univariate and multivariate Cox proportional-hazards regression model, including non-adjusted model (no covariates were adjusted), minimally-adjusted model (only sociodemographic variables were adjusted) and fully-adjusted model (covariates presented in Table 1 were adjusted). Effect sizes with 95% confidence intervals were recorded. Because Cox proportional-hazards regression model based methods are often suspected for their inability to deal with non-linear

models. For that reason, nonlinearity between HbA1c and coronary artery calcium score progression were addressed using Cox proportional hazards regression model with cubic spline functions and the smooth curve fitting (penalized spline method). If nonlinearity was detected, we firstly calculated the inflection point using recursive algorithm, and then constructed a two-piecewise Cox proportional-hazards regression model on both sides of the inflection point.

Table 1
Baseline characteristics of participants(N = 8151)

	coronary artery calcium score progression		
	NO	YES	P-value
N	3050	5101	
HbA1c, mean ± sd, (%)	5.50 ± 0.60	5.73 ± 0.82	< 0.001
Sex, (n, %)			0.046
Male	2750 (90.16%)	4666 (91.47%)	
Female	300 (9.84%)	435 (8.53%)	
Age group, (n, %)			< 0.001
< 65	2914 (95.54%)	4417 (86.59%)	
>=65	136 (4.46%)	684 (13.41%)	
Duration	3.72 ± 2.02	3.97 ± 2.23	< 0.001
BMI, mean ± sd, (kg/m ²)	24.40 ± 2.48	24.93 ± 2.59	< 0.001
Height, mean ± sd, (cm)	169.91 ± 6.73	169.15 ± 6.62	< 0.001
Weight, mean ± sd, (kg)	70.59 ± 9.37	71.46 ± 9.50	< 0.001
SBP, mean ± sd, (mmHg)	117.41 ± 15.14	120.57 ± 15.77	< 0.001
DBP, mean ± sd, (mmHg)	74.76 ± 10.50	76.27 ± 10.52	< 0.001
TC, mean ± sd, (mg/dL)	197.31 ± 33.01	199.34 ± 34.79	0.009
LDL-C, mean ± sd, (mg/dL)	127.30 ± 30.06	128.90 ± 31.46	0.024
HDL-C, mean ± sd, (mg/dL)	52.61 ± 12.86	51.41 ± 12.55	< 0.001
Triglycerides, median (Q1-Q3), (mg/dL)	121.00 (86.00-171.00)	150.58 ± 90.51	< 0.001
Smoking status, (n, %)			< 0.001
Never	885 (34.25%)	1276 (28.62%)	
Past smoker	916 (35.45%)	1837 (41.21%)	
Current smoker	783 (30.30%)	1345 (30.17%)	
Alcohol consumption, (n, %)			0.018

HbA1c, glycated hemoglobin; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CAC-P, coronary artery calcium score progression. The data presented are the means ± standard deviations, median (Q1-Q3) or numbers (percentages).

	coronary artery calcium score progression	
Never	369 (12.97%)	723 (14.90%)
Past drinker	39 (1.37%)	88 (1.81%)
Current drinker	2436 (85.65%)	4041 (83.29%)
Reflux esophagitis status, (n, %)		0.002
Negative	2729 (89.48%)	4446 (87.16%)
Positive	321 (10.52%)	655 (12.84%)
Hypertension, n(%)		< 0.001
Negative	2878 (94.36%)	4642 (91.00%)
Positive	172 (5.64%)	459 (9.00%)
Diabetes, n(%)		< 0.001
Negative	2987 (97.93%)	4925 (96.55%)
Positive	63 (2.07%)	176 (3.45%)
Dyslipidemia, n(%)		0.012
Negative	2876 (94.30%)	4737 (92.86%)
Positive	174 (5.70%)	364 (7.14%)
Ischemic heart disease, n(%)		0.032
Negative	3045 (99.84%)	5078 (99.55%)
Positive	5 (0.16%)	23 (0.45%)
Cerebrovascular disease n(%)		0.996
Negative	3047 (99.90%)	5096 (99.90%)
Positive	3 (0.10%)	5 (0.10%)
HbA1c, glycated hemoglobin;BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC,total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CAC-P, coronary artery calcium score progression. The data presented are the means ± standard deviations, median (Q1-Q3) or numbers (percentages).		

To test the robustness of our results, we performed a sensitivity analysis. We converted HbA1c into a categorical variable according to the quartile, and calculated the P for trend in order to verify the results of HbA1c as the continuous variable, and to examine the possibility of nonlinearity.

Modeling was performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Inc, Boston, MA). P values less than 0.05 (two-sided) were considered statistically significant.

Results

Baseline characteristics of participants

The baseline characteristics of these included participants were listed in Table 1. The average age was 53.82 ± 7.66 years old and about 90.98% were male. The incidence of progression was 62.58% (5101/8151). For all variables in Table 1, except cerebrovascular disease, there were statistically significant differences between the no progression group and the progression group (P values < 0.05). When compared with no progression group, HbA1c, age, sex, duration, BMI, weight, SBP, DBP, TC, LDL-C, triglycerides, smoking status, alcohol consumption, reflux esophagitis status, hypertension, diabetes, dyslipidemia, ischemic heart disease and cerebrovascular disease increased significantly in the progression group, while the opposite results were detected in covariates in terms of height and HDL-C.

The results of multivariate analyses using Cox proportional-hazards regression model

To evaluate the correlation between HbA1c and coronary artery calcium score progression, three models (Cox proportional-hazards regression model) were constructed (Table 2). In un-adjusted model, an increase of 1 % of HbA1c was related with 24% increases of risk of coronary artery calcium score progression (HR = 1.24, 95%CI: 1.20 to 1.27). The results was statistically significant. In minimally-adjusted model, when we only adjusted for demographic variables, each additional 1% of HbA1c increases by 23% (HR = 1.23, 95%CI: 1.19 to 1.26). In fully-adjusted model, Each additional 1% of HbA1c was accompanied by a 22% increases in coronary artery calcium score progression (HR = 1.22, 95%CI: 1.18 to 1.26). The distribution of confidence intervals indicated that the link between HbA1c and coronary artery calcium score progression obtained by the model was reliable.

Table 2
Univariate and multivariate analyses of the association between HbA1c and coronary artery calcium score progression

Variable	Non-adjusted model HR (95%CI)	Minimally-adjusted model HR (95%CI)	Fully-adjusted model HR (95%CI)
HbA1c (%)	1.24 (1.20, 1.27)	1.23 (1.19, 1.26)	1.22 (1.18, 1.26)
HbA1c group			
Q1	1.0	1.0	1.0
Q2	1.33 (1.21, 1.45)	1.32 (1.20, 1.44)	1.42 (1.29, 1.56)
Q3	1.61 (1.47, 1.76)	1.57 (1.44, 1.72)	1.63 (1.48, 1.80)
Q4	2.01 (1.85, 2.19)	1.92 (1.77, 2.10)	1.98 (1.80, 2.17)
P for trend	< 0.0001	<0.0001	<0.0001
HR, Hazards ratio; CI, confidence interval;HbA1c, glycated hemoglobin			
Non-adjusted model: we do not adjusted for any variates			
Minimally-adjusted model: only sex and age are adjusted for			
Fully-adjusted model: all variates presented in Table 1 are adjusted for			

The nonlinearity addressing by Cox proportional hazards regression model with cubic spline functions

Through the Cox proportional hazards regression model with cubic spline functions and smooth curve fitting, we observed that the correlation between HbA1c and coronary artery calcium score progression was nonlinear (Fig. 2). For that reason, data were fit to a piecewise Cox proportional-hazards regression model to fit two different slopes. Based on the sensitivity analysis, we also fit data by standard Cox proportional-hazards regression model, and selected the best fit model through log-likelihood ratio test (Table 3). In our study, the P for log-likelihood ratio test was less than 0.05, we hence used two-piecewise model to fitting the association between HbA1c and coronary artery calcium score progression. By recursive algorithm, we first obtained the inflection point was 5.8, and then calculated the effect sizes and confidence interval on the left and right of the inflection point by two-piecewise Cox proportional-hazards regression model. On the left side of inflection point, the effect size and 95%CI were 2.05, 1.85 to 2.27, respectively. On the right side of inflection point, the effect size and 95%CI were 1.04, 0.99 to 1.10, respectively.

Table 3
 Nonlinearity explanation on HbA1c and coronary artery calcium score progression using two-piecewise linear model

	Effect size (95%CI) P value
Fitting model by standard linear regression	1.22 (1.18, 1.26) < 0.0001
Fitting model using two-piecewise linear model	
Inflection point	5.8
< 5.8	2.05 (1.85, 2.27) <0.0001
> 5.8	1.04 (0.99, 1.10) 0.1123
P for log-likelihood ratio test	< 0.001
The adjustment strategy is the same with fully-adjusted model	

Discussion

In this observational retrospective cohort study, we found a nonlinear saturation effect between HbA1c and the progression of coronary artery calcium score. When HbA1c was less than 5.8, there was a positive correlation between HbA1c and the progression of coronary artery calcium score, while above 5.8, this positive correlation tended to be saturated. Even if HbA1c increased again, the risk of coronary artery calcium score progression would not increase.

Some previous studies have shown the consistent results with ours investigating correlation between HbA1c and coronary artery calcium score progression or coronary atherosclerosis. Based on 411 patients without history of known diabetes mellitus, Reza Ajudani reported that HbA1c may be an independent diagnostic factor in non-diabetic patients with severe coronary atherosclerosis in a cross-sectional study[19]. Besides, Wenhui Zhao et al. used African American and white diabetic patients as the study population and obtained similar results[20]. Rivera JJ et al. reached similar conclusions in 1043 asymptomatic people without diabetes[21]. In addition, in veterans affairs diabetes trial participants, Peter D Reaven et al. found that although intensive hypoglycemic therapy did not reduce cardiovascular events in the study cohort as a whole, intensified hypoglycemic therapy could reduce cardiovascular events in people with less severe coronary atherosclerosis[22]. However, it is not that lower HbA1c level is associated with better the occurrence and outcome of cardiovascular events. Hertz C Gerstein et al. reported that using intensive therapy to position glycosylated hemoglobin levels below 6.0% could increase mortality, but did not significantly reduce major cardiovascular events in type 2 diabetes[23]. The inconsistency of these studies may be due to the small sample size, different study population, different forms of outcome variables and few cases of coronary heart disease, which may limit statistical power.

Our study has some strengths, and we listed it as follows. First, the sample size of

this study was relatively large. Second, previous articles that also studied HbA1c and coronary artery calcium score or coronary atherosclerosis did not clarify the nonlinear relationship [19, 20, 24–29]. To the best of our knowledge, this is the first time that a non-linear relationship has been reported and an inflection point has been determined and explained in exploring the correlation between HbA1c and coronary artery calcium score progression. Third, this study is an observational study and therefore susceptible to potential confounding. We used strict statistical adjustment to minimize residual confounders. Fourth, we ensured the robustness of the results through sensitivity analysis (conversion of target independent variable form). This makes our results more reliable.

Our research has the following shortcomings and needs attention. Firstly, our findings can be generalized to persons who had undergone physical examinations at South Korea only. Secondly, due to the limitation of the original data, we could not observe the correlation between HbA1c and the progress of coronary artery calcium score in diabetes and prediabetes patients. Finally, as in all observational studies, even though known potential confounders factors were controlled for, there might have been still uncontrolled confounders.

Conclusion

The relationship between HbA1c and coronary artery calcium score progression is non-linear. HbA1c is positively related with coronary artery calcium score progression when HbA1c was less than 5.8%.

Abbreviations

HbA1c: glycated hemoglobin; CHD: coronary heart disease; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; EGD: esophagogastroduodenoscopy; CT: coronary computed tomography

Declarations

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Authors' contributions

JY contributed to the drafting of the manuscript, and analysis and interpretation of the data. BG contributed to the conception and critical revision of the manuscript, analysis and interpretation of the data and approved the final version of the submitted manuscript. Both authors read and approved the final manuscript.

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Availability of data and materials

Data can be downloaded from the "PLOS ONE" database (<https://journals.plos.org/plosone/>).

Ethics approval and consent to participate

In the previously published article [17], Yang Won Min, et al. has clearly stated that: the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all Participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

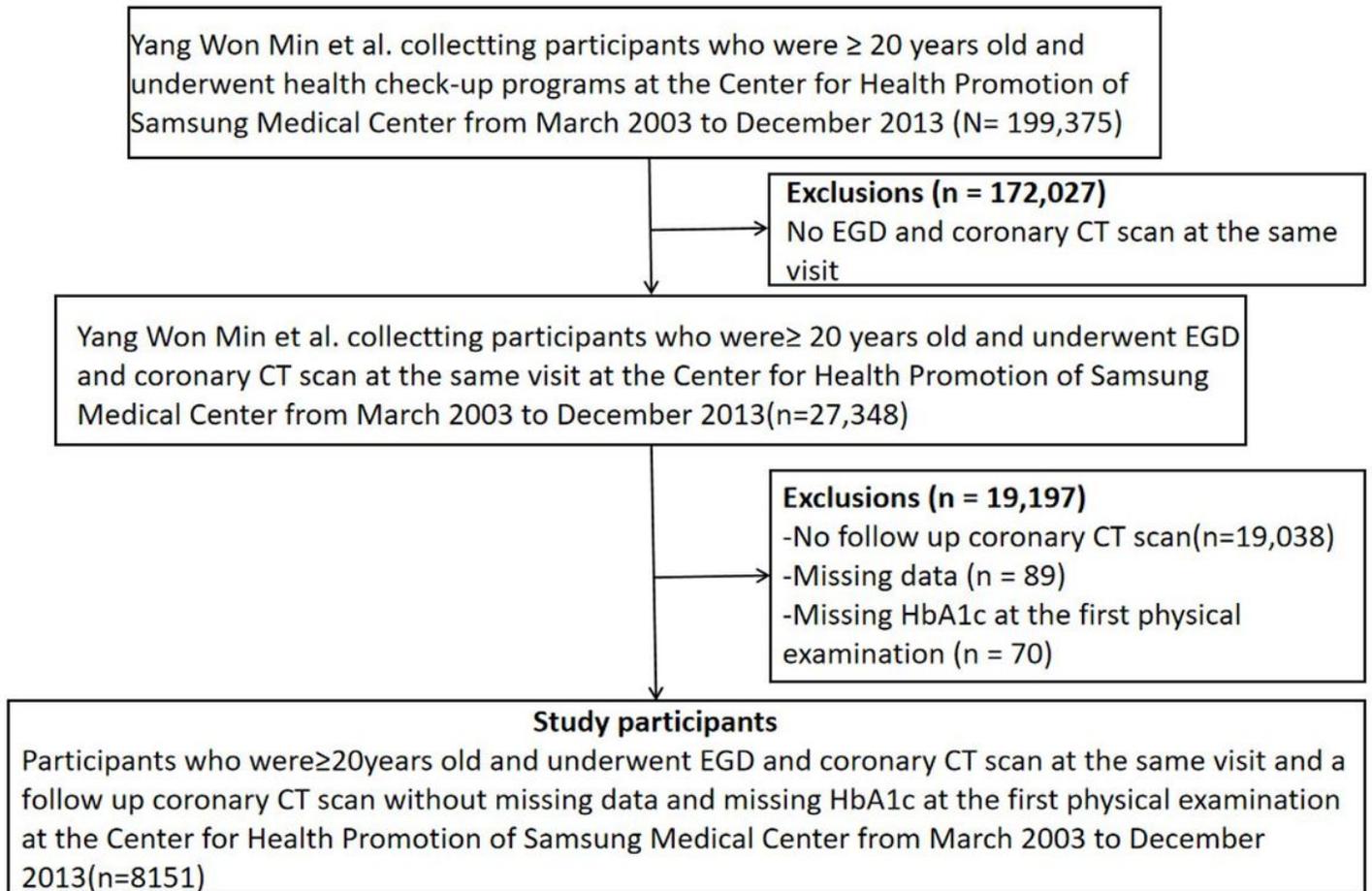


Figure 1

Study flow chart. EGD, esophagogastroduodenoscopy; CT, computed tomography

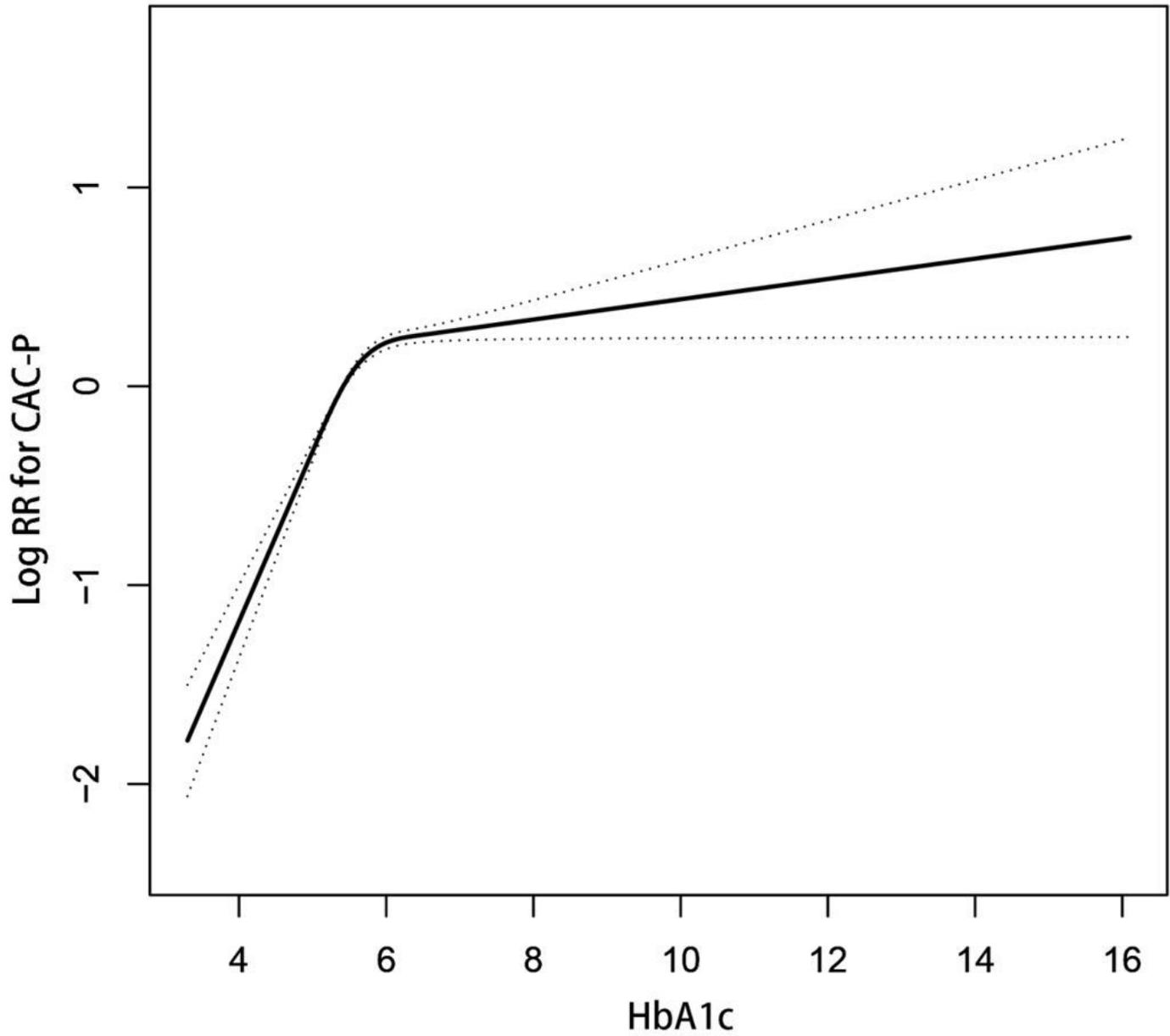


Figure 2

Relationship between HbA1c and coronary artery calcium score progression by using Lowess smoothing technique. HbA1c, glycated hemoglobin; CAC-P,coronary artery calcium score progression