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Association between O-GlcNAc transferase activity and major adverse cardiovascular events: findings from the China PEACE-MPP cohort

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Abstract

Background The O-GlcNAc transferase (OGT) levels are closely related to the O-GlcNAcylation of proteins and are also associated with cardiovascular disease. This study explored the association between OGT activity and major adverse cardiovascular events (MACEs) in patients with high cardiovascular disease risk. This post hoc study included patients from the China PEACE-MPP study in Yi Wu, Zhejiang Province, between 2014 and 2015.

Methods The patients were divided into the low and high OGT activity groups according to the median serum OGT value. The outcome was the occurrence of MACEs (cardiovascular death, non-fatal acute myocardial infarction, and non-fatal ischemic stroke).

Results Finally, 1947 participants (973 and 974 with low and high OGT activity, respectively) were included. The mean follow-up was 5.56 ± 1.01 years. The participants in the low OGT activity group had a significantly higher occurrence rate of MACEs compared with the high OGT activity group (100 [10.4%] vs. 74 [7.6%], $P = 0.032$). The Kaplan-Meier analysis showed that the event-free survival rate in the low OGT activity group was significantly lower than in the high OGT activity group ($P = 0.036$). Multivariable Cox proportional hazards regression analysis showed that after adjustment for age, drinking, hyperglycemia, history of hypertension, and history of cardiovascular and cerebrovascular disease, a high OGT activity was independently associated with a lower risk of MACEs (HR = 0.738, 95%CI: 0.547–0.997, $P = 0.048$).

Conclusions A low OGT activity was independently associated with an increased risk of MACE among patients with a high risk of cardiovascular disease.

Trial registration Not applicable.

Keywords Major adverse cardiovascular events, Cardiovascular diseases, Screening, Serum marker, O-GlcNAc transferase

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Background

Cardiovascular diseases (CVD) rank first as the cause of death and disability in the world [1–3]. Early screening and treatment of individuals with high cardiovascular risk are crucial to reducing the incidence, morbidity, and mortality of CVD [4, 5]. The CVD risk prediction models released by various countries and authoritative organizations consider people with a high risk of major adverse cardiovascular events (MACE) (such as risk ≥ 20%) over a certain period (such as 10 years) as high-risk subjects to be focused on and treated early [4, 6–8]. These models include various risk factors and algorithms, and the definitions of high-risk subjects differ. In addition, these risk prediction models have limitations that do not allow quantitative and dynamic prediction of exposure to risk factors. Therefore, exploring convenient, precise, and biologically/functionally relevant cardiovascular risk markers is clinically important.

O-GlcNAcylation (O-GlcNAc) mediated by the activation of the hexosamine pathway is a ubiquitous protein post-translational regulation, i.e., a "metabolic regulator" that affects various systems throughout the body [9–11]. Proteins with O-GlcNAc have been found in body fluids such as serum [12] and urine [13]. In recent years, accumulating evidence supports a relationship between O-GlcNAc and CVD [14–17]. Still, available data on O-GlcNAc mostly focus on identifying the proteins targeted by O-GlcNAc and the downstream signaling pathways and biological effects that could be pharmaceutical targets [18].

The O-GlcNAc transferase (OGT) is a key enzyme for transferring the O-GlcNAc group from substrates to amino acid sites of proteins. The OGT activity is closely related to the O-GlcNAc of proteins and is also associated with CVD [15–17]. An enzyme-linked immunosorbent assay (ELISA) was developed to determine the activity level of OGT in the serum [19]. Therefore, this post hoc analysis of a prospective cohort study aimed to explore the association between OGT activity and MACEs in patients with high CVD risk.

Methods

Study design and patients

This post hoc analysis of a prospective cohort study included patients from the China Patient-centered Evaluative Assessment of Cardiac Events (PEACE) Million Persons Project (MPP) study enrolled in Yi Wu, Zhejiang Province, between 2014 and 2015 [20]. The China PEACE-MPP began in July 2014 in four provinces in China, which were chosen according to their locally available human resources and capacity to perform large-scale screening.

The inclusion criteria for the China PEACE-MPP were (1) aged 40–75 and (2) registered in the Hukou (which is a record officially identifying a person as a resident of an area) of the selected regions. The inclusion criteria for this study were (1) participation in the China PEACE-MPP in Yi Wu County, Zhejiang Province, and (2) defined as high CVD risk. High CVD risk was defined as meeting at least one of the following criteria: (1) a history of established CVD, (2) systolic blood pressure (SBP) ≥ 160 mmHg or diastolic blood pressure (DBP) ≥ 100 mmHg, (3) low-density lipoprotein-cholesterol (LDL-C) ≥ 160 mg/dL (4.14 mmol/L), (4) high-density lipoprotein-cholesterol (HDL-C) < 30 mg/dL (0.78 mmol/L), and (5) a 10-year risk of CVD ≥ 20% assessed using the World Health Organization (WHO) and International Society of Hypertension Risk Prediction charts [20].

The exclusion criteria were (1) incomplete baseline survey data or (2) Log_{10}(OGT) outside the mean ± 3 standard deviations of the study population.

This study was approved by the Medical Ethics Committee of Zhejiang Hospital (2018 11 K), and the requirement for informed consent was waived because of the study's retrospective nature. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration.

Data collection and outcomes

The history of CVD was based on self-reported data on the history of at least one of the following cardiovascular events, as in the original China PEACE-MPP study [20]: myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, or stroke (irrespective of ischemic or hemorrhage). The baseline survey data included cardiovascular health, blood pressure, height, weight, waist circumference, and rapid blood glucose and lipid tests. The participants were asked using a standardized, face-to-face electronic questionnaire about their smoking status. They indicated whether they were never, former, or current smokers. In addition, for those with any smoking history, details were obtained on frequency, cigarette type, and quantity of tobacco consumed daily [20]. In the present study, smoking was defined as currently smoking at study entry. The participants were asked how often they consumed alcohol, with response options including "never," "monthly or less," "2–4 times a month," "2–3 times a week," or "over 4 times a week." Former drinkers were also queried about their typical alcohol consumption on a regular drinking day (from which an average daily alcohol intake could be calculated) [20]. Here, drinking was defined as drinking any amount of alcohol (i.e., all participants except "never"). In this study, cardiovascular events were assessed by self-reporting and further clinical data collection. Events such as myocardial infarction and stroke were captured, with stroke

typically representing the cerebrovascular component of cardiovascular disease. Stroke included both ischemic and hemorrhagic types [20].

For the serum OGT activity assay, 4 mL of fasting venous blood was collected. After centrifugation, serum was aliquoted and stored at -80 °C. The serum OGT activity was determined by ELISA using a commercial OGT kit (Shanghai Xinyu Biotechnology, Shanghai, China) according to the manufacturer's instructions. The plate was read on a microplate reader at 450 nm using the blank well as zero. A standard curve was created according to the concentrations and optical density values of the standards. Then, the OGT activity was calculated according to the standard curve. OGT activity was log-converted, and $\log_{10}$(OGT) was used for the analysis. Values outside the mean ± 3 standard deviations were excluded as outliers. Log_{10}(OGT) showed a normal distribution according to the Kolmogorov-Smirnov test. The participants were divided into the low and high OGT activity groups. Gigh OGT activity was defined as being above the median value (935.6 ng/L; range: 105.77-20,233.27 ng/L; Q1-Q3: 678.51-1337.75 ng/L).

High-risk subjects were followed up either in a return clinic visit or by telephone interview. Follow-up included measurement of blood pressure, weight, electrocardiogram (ECG), and questionnaires on survival status, hospitalizations, and lifestyle habits [20]. The outcome of this study was the occurrence of MACE. The participants were enrolled in the cohort after baseline surveys from 2014 to 2015. We collected the MACEs of cardiovascular death, non-fatal acute myocardial infarction, and non-fatal ischemic stroke. The data were derived from the CVD reporting database of the Zhejiang Provincial Center for Disease Control and Prevention. The follow-up was censored on December 31, 2020.

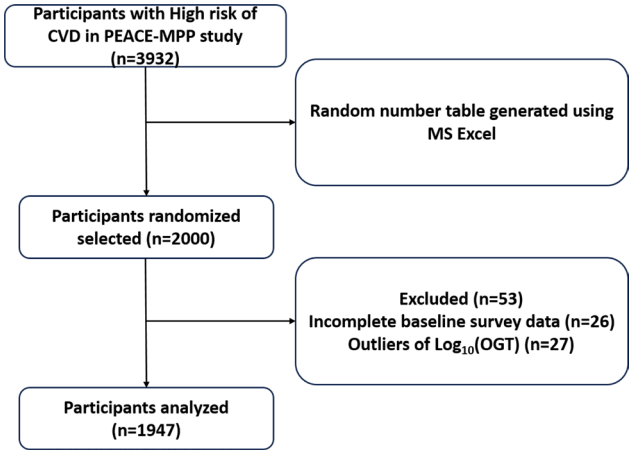

Fig. 1 Flowchart for participants selection. The outliers of Log_{10}(OGT) were defined as Log_{10}(OGT) being outside the mean ± 3 standard deviations of the study population. CVD: Cardiovascular diseases. PEACE-MPP: Patient-centered Evaluative Assessment of Cardiac Events Million Persons Project. OGT: O-GlcNAc transferase

Statistical analysis

According to the annual chronic diseases monitoring report in Zhejiang Province for 2013–2018, the cumulative incidence of acute coronary events in the whole population over the 6 years was 294.42 per 100,000 individuals, the incidence of acute stroke was 2047.86 per 100,000 individuals, and the cumulative incidence of MACE over the 6 years was 2300 per 100,000 individuals. Therefore, it was estimated that the cumulative incidence of MACE in middle-aged and older adults over 40 years old over 6 years was not less than 3000 per 100,000 individuals. The preset relative risk of the high-value OGT group and the low-value OGT group was 0.5, and the power was 80%. Hence, at least 1601 cases were required. Considering an invalid rate of 20%, data from 2000 patients were collected. Since the number of patients was larger than 2000, the 2000 participants were selected using simple randomization based on a random number table generated using MS Excel.

SPSS 22.0 (IBM, Armonk, NY, USA) was used for analysis. The continuous data were expressed as means ± standard deviations and compared using Student's t-test. The categorical variables were expressed as n (%) and compared using the chi-squared test. Kaplan-Meier survival curves were used to analyze the survival rates between the two groups without MACE, and the log-rank test was used to evaluate the differences between curves. The univariable Cox proportional hazards regression model was used to analyze the factors influencing MACE, and the relevant influencing factors (i.e., $P < 0.05$) were included in the multivariable Cox proportional hazards regression analysis. Two-sided P-values < 0.05 were considered statistically significant.

Results

In the PEACE-MPP study, 3932 participants were judged to be with high risk of CVD at the initial screening. Then, 2000 participants were selected randomly for the present study. Among the 2000 participants, those without complete baseline survey data were excluded ($n = 26$). In addition, 27 participants were excluded for Log_{10}(OGT) being outside the mean ± 3 standard deviations of the study population (Fig. 1). The baseline data of the 1947 participants are shown in Table 1. Compared with the high OGT activity group, there were significantly fewer females (47.3% vs. 56.2%, $P < 0.001$) and patients with hypercholesterolemia (46.6% vs. 52.4%, $P = 0.010$) in the low OGT activity group. In addition, the participants in the low OGT activity group had significantly lower LDL-C levels ($P = 0.005$), and there were significantly more smokers ($P = 0.027$), obese ($P = 0.034$), and

Table 1 Cardiovascular disease characteristics between two groups

Characteristics	Low OGT activity group (*n* = 973)	High OGT activity group (*n* = 974)	All (*n* = 1947)	*P*
OGT (ng/L)	663.71 ± 165.82	1643.73 ± 887.01	1153.97 ± 804.59	**< 0.001**
Female, n (%)	460 (47.3%)	547 (56.2%)	1007 (51.7%)	**< 0.001**
Age (years)	59.46 ± 9.09	59.14 ± 9.21	59.30 ± 9.15	0.623
Smoking, n (%)	177 (18.2%)	141 (14.5%)	318 (16.3%)	**0.027**
Drinking, n (%)	187 (19.2%)	165 (16.9%)	352 (18.1%)	0.191
Body mass index (kg/m^2)	25.28 ± 3.19	24.88 ± 3.2	25.08 ± 3.2	0.564
Obesity, n (%)	183 (18.8%)	148 (15.2%)	331 (17.0%)	**0.034**
SBP (mmHg)	159.67 ± 19.46	159.17 ± 20.9	159.42 ± 20.19	0.092
High SBP, n (%)	804 (82.6%)	785 (80.6%)	1589 (81.6%)	0.246
DBP (mmHg)	88.10 ± 12.08	87.51 ± 12.41	87.80 ± 12.25	0.257
High DBP, n (%)	430 (44.2%)	426 (43.7%)	856 (44.0%)	0.839
TC (mmol/L)	5.29 ± 1.44	5.53 ± 1.43	5.41 ± 1.44	0.745
Hypercholesterolemia, n (%)	453 (46.6%)	510 (52.4%)	963 (49.5%)	**0.010**
LDL-c (mmol/L)	2.95 ± 1.19	3.05 ± 1.3	3.00 ± 1.25	**0.005**
High LDL-c, n (%)	263 (27%)	301 (30.9%)	564 (29.0%)	0.060
HDL-c (mmol/L)	1.37 ± 0.48	1.44 ± 0.46	1.41 ± 0.47	0.175
Low HDL-c, n (%)	263 (27.0%)	183 (18.8%)	446 (22.9%)	**< 0.001**
TG (mmol/L)	2.41 ± 1.33	2.43 ± 1.33	2.42 ± 1.33	0.574
Hypertriglyceridemia, n (%)	606 (62.3%)	617 (63.3%)	1223 (62.8%)	0.627
Fasting blood glucose (mmol/L)	6.25 ± 2.27	6.17 ± 1.88	6.21 ± 2.08	0.142
Hyperglycemia, n (%)	150 (15.5%)	154 (15.9%)	304 (15.7%)	0.826
History of hypertension, n (%)	438 (45%)	428 (43.9%)	866 (44.5%)	0.634
History of diabetes, n (%)	120 (12.3%)	103 (10.6%)	223 (11.5%)	0.223
History of AMI, n (%)	7 (0.7%)	12 (1.2%)	19 (1.0%)	0.250
History of stroke, n (%)	60 (6.2%)	47 (4.8%)	107 (5.5%)	0.194
History of cardiovascular and cerebrovascular disease, n (%)	89 (9.1%)	72 (7.4%)	161 (8.3%)	0.160

OGT: O-GlcNAc transferase; TC: total cholesterol; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; TG: triglycerides; FBS: fasting blood glucose; AMI: acute myocardial infarction; SBP: systolic blood pressure; DBP: diastolic blood pressure

High SBP: SBP ≥ 140 mmHg; high DBP: DBP ≥ 90 mmHg; hypercholesterolemia: TC ≥ 5.2 mmol/L; high LDL-c: LDL-c ≥ 3.4 mmol/L; low HDL-c: HDL-c < 1.04 mmol/L; hypertriglyceridemia: TG ≥ 1.7 mmol/L; hyperglycemia: fasting blood glucose ≥ 7.0 mmol/L; obesity: BMI ≥ 28 kg/m^2

Table 2 Occurrence of MACE

Characteristics	Low OGT activity group (*n* = 973)	High OGT activity group (*n* = 974)	All (*n* = 1947)	*P*
Cardiovascular death, n (%)	2 (0.2%)	5 (0.5%)	7 (0.4%)	0.528
Stroke	89 (9.1%)	65 (6.7%)	154 (7.9%)	0.043
AMI, n (%)	10 (1.0%)	4 (0.4%)	14 (0.7%)	0.107
MACE, n (%)*	101 (10.4%)	74 (7.6%)	175 (9.0%)	0.032
Duration of follow-up (years)*	5.54 ± 1.07	5.58 ± 0.94	5.56 ± 1.01	0.004

*$P < 0.05$ between the two groups

OGT: O-GlcNAc transferase; AMI: acute myocardial infarction; MACE: major adverse cardiovascular event

participants with low HDL-C levels ($P < 0.001$) compared with the high OGT activity group. The two groups had no significant differences in age, history of cardiovascular and cerebrovascular disease, blood pressure, blood glucose, total cholesterol, and triglycerides.

The mean follow-up time for the 1947 participants was 5.56 ± 1.01 years. Compared with the high OGT activity group, the low OGT activity group showed a higher occurrence of MACEs (10.4% vs. 7.6%, $P = 0.032$) but without significant differences for the individual components of MACEs (Table 2). A survival curve analysis was performed on MACEs between the two groups (Fig. 2). The cumulative non-incidence of MACE (survival) rate in the low OGT activity group was significantly lower than in the high OGT activity group ($P = 0.036$).

The occurrence of MACE was taken as the dependent variable, and the influencing factors of MACE were analyzed using Cox regression. First, the relevant factors, including OGT activity, sex, age group (per 10 years old), smoking, drinking, hypertension, diabetes, myocardial infarction, stroke, history of cardiovascular and cerebrovascular disease, obesity, dyslipidemia, elevated blood glucose, elevated blood pressure, etc., were analyzed using univariable Cox regression, suggesting that OGT activity, age group, drinking, hyperglycemia, and related medical history (hypertension, stroke, and cardiovascular

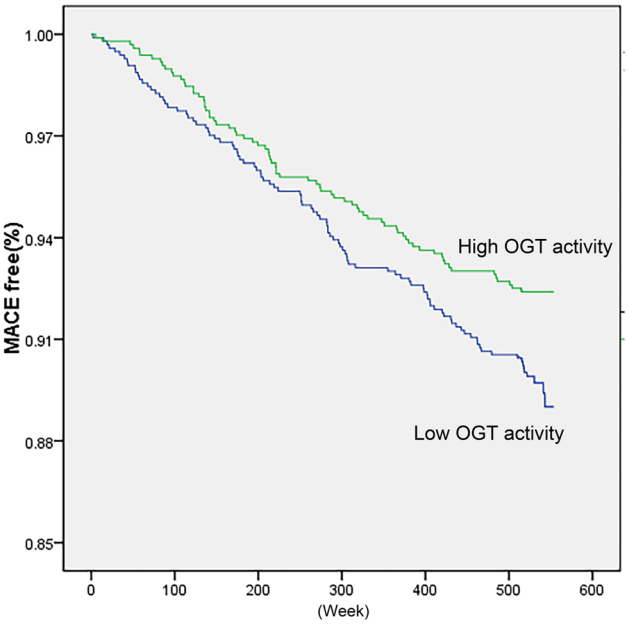

Fig. 2 Kaplan-Meier survival curves of major adverse cardiovascular events (MACEs). The differences between the two curves were statistically significant (log-rank, $P=0.036$). OGT: O-GlcNAc transferase

Table 3 Multivariable Cox regression parameters of MACE

OGT activity	HR (95%CI)	*P*
Low	Reference	-
High	0.738 (0.547, 0.997)	0.048

HE: hazard ratio; CI: confidence interval; OGT: O-GlcNAc transferase

Adjusted for age, drinking, hyperglycemia, history of hypertension, and history of cardiovascular and cerebrovascular disease

and cerebrovascular disease) were influencing the occurrence of MACE (all $P<0.05$).

These factors were included in the multivariable Cox regression model. Covariant factors (such as a history of stroke being covariant with a history of cardiovascular and cerebrovascular disease) were excluded. After adjustment for age, drinking, hyperglycemia, history of hypertension, and history of cardiovascular and cerebrovascular disease, a high OGT activity was independently associated with a lower risk of MACEs (HR = 0.738, 95%CI: 0.547–0.997, $P=0.048$) (Table 3). Compared with participants ≥ 65 years, the risk of MACE of participants of 45–54 years and 55–64 years was significantly decreased (HR = 0.384 and HR = 0.617, respectively, $P<0.05$).

Discussion

The results suggest that a low OGT activity was independently associated with an increased risk of MACE among patients with high CVD risk. Hence, in patients with high cardiovascular risk, OGT activity could be used to screen individuals with a higher risk of MACE.

Both elevated blood glucose in vivo and administration of glucose in vitro can activate the hexosamine pathway. Uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), as a downstream product, transfers the GlcNAc group to the serine/threonine carboxyl group catalyzed by OGT, an important protein post-translational modification (PTM). It was found that the deletion of OGT in fat cells can lead to decreased O-GlcNAc and increased phosphorylation of lipid-droplet-related perilipin-1 (PLIN1), which promotes fat decomposition. The overexpression of OGT can inhibit lipolysis, suggesting the potential of OGT-targeted interventions in treating obesity [21].

O-GlcNAc occurs mainly in nucleoproteins and cytoplasm, limiting non-invasive clinical studies. Still, O-GlcNAc can be measured in peripheral blood and body fluids. Myslicki et al. [12] measured O-GlcNAc levels and OGT activity of serum proteins in healthy young adults aged 18–35 years and found that the O-GlcNAc level was more sensitive for screening for insulin resistance than glycated hemoglobin (HbA1c). Shen et al. [13] reported O-GlcNAc in human urine for the first time. The present study also showed O-GlcNAc and OGT in serum samples, which might be derived from blood cells, including red blood cells and white blood cells, or even from disrupted endothelial cells.

MACEs include non-fatal acute myocardial infarction, non-fatal ischemic stroke, and death from CVD, all of which share atherosclerosis as the main pathogenic mechanism. O-GlcNAc plays an important role in atherosclerotic lesions and is involved in the atherosclerotic pathological process of multiple signaling pathways [18]. Recently, the potential role of O-GlcNAc has been reported in hypertension [22], and O-GlcNAc regulates the interleukin 10 (IL-10) signaling pathway to inhibit the protective effect of IL-10 on blood vessels [23]. O-GlcNAcylation reduces the vasoprotective function of endothelial nitric oxide synthase (eNOS) while increasing the transcription of atherosclerotic genes such as Thrombospondin 1 (TSP-1) [24]. In a mouse model of atherosclerosis, it was found that IL-17 A produced by $CD4^+$ Th17 cells and signaling pathway regulation of IL-17 A might play an important role in the pathogenesis of atherosclerosis [25, 26]. Elevated levels of Th17 cells are found in obese patients, and O-GlcNAc of $CD4^+$ T cells in diet-induced obese mice is upregulated, promoting the increase of IL-17 A [27]. Narayanan et al. [28] also reported that elevated O-GlcNAc in female mice contributed to reduced heart ischemic susceptibility.

The present study assessed the OGT activity in people with a high risk of CVD and analyzed the predictive effect on MACEs at 6 years, showing that low OGT activity might lead to an increased risk of MACE. Although the source of OGT in the blood and its mechanisms are

unclear, this study might provide some direction for research. The causes of atherosclerosis are various, and metabolic diseases such as abnormal blood glucose and lipid metabolism are the most important causes. The activation of the hexosamine pathway and O-GlcNAc are recognized metabolic regulators that must play an indispensable role in atherosclerosis. About 2000 patients with high cardiovascular risk were enrolled in this study, including patients with cardiovascular and cerebrovascular diseases, patients with blood pressure grade ≥ 2, patients with obvious abnormal blood lipids, or high-risk patients assessed by the WHO risk model. Male, decreased HDL-C, and elevated body mass index (BMI) were associated with decreased OGT activity. The 6-year follow-up cohort study showed an overall increased risk of MACEs (including non-fatal acute myocardial infarction, non-fatal ischemic stroke, and cardiovascular death) in patients with low OGT activity. Still, conflicting results have been reported so far. Indeed, Umapathi et al. [16] reported that excessive O-GlcNAc led to cardiomyopathy in mice due to defective energy metabolism. The review by Wang et al. [14] highlights that the disturbances in O-GlcNAc lead to disturbances in gene transcription, energy metabolism, and signal transduction but that the role of O-GlcNAc in the pathogenesis of CVD remains controversial. As reviewed by Wright et al. [15], increased O-GlcNAc in diabetes appears to be involved in the development of CVD, but high O-GlcNAc levels appear protective in ischemia/reperfusion injury, and O-GlcNAc appears to be required for the normal function and homeostasis of the cells. Therefore, the clinical meaning of the changes in O-GlcNAcylation could be highly dependent upon the characteristics of the studied population. Therefore, large-scale studies are necessary to examine the factors influencing O-GlcNAc and how CVD risk factors and patient characteristics interact with O-GlcNAc to increase the risk of MACEs.

When looking at the entire patient population with CVD, a main feature is that the patients display wide variations in clinical and laboratory characteristics; furthermore, even patients sharing similar characteristics will have different prognoses [29]. Several scores tried to quantify the variability among patients and refine prognostication, such as the Thrombolysis in Myocardial Infarction (TIMI) risk score, the Global Registry of Acute Coronary Events (GRACE) score, the SYNergy between PCI with TAXUS™ and Cardiac Surgery (SYNTAX) score, and HEART score [30–32]. Although these scores allow a refinement of the prognostication of CVD, they remain imperfect and need refinement. One way to refine them might be to combine them with non-traditional risk factors for MACE, such as OGT activity. Future studies should investigate multivariable prognostic models that include OGT activity for the prediction of MACE.

This study has some limitations. Although it was performed in a large sample size, it was still too small to perform subgroup analyses based on comorbidities because the incidence of MACEs was relatively low, resulting in too small numbers of events in some subgroups. In addition, the development of MACEs is a slow process, even in high-risk patients, and a follow-up of only 6 years was probably too short. O-GlcNAc appears to be involved in inflammation [11], and inflammation is involved in atherosclerosis [33], but inflammation parameters were not measured. There are no universally accepted cutoff points for OGT activity [15–17], which is a common limitation of all clinical studies on OGT activity. The lack of a recognized cutoff point limits comparability among studies, and future studies should aim at determining a clinical cutoff value.

Conclusions

In conclusion, the results suggest that a low OGT activity was independently associated with an increased risk of MACE among patients with a high risk of CVD. The present study was the first to investigate the application of serum O-GlcNAc and OGT activity for population screening and CVD risk prediction.

Abbreviations

BMI	Body Mass Index
CVD	Cardiovascular Diseases
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ELISA	Enzyme-Linked Immunosorbent Assay
eNOS	Endothelial Nitric Oxide Synthase
GRACE	Global Registry of Acute Coronary Events
HbA1c	Glycated Hemoglobin
HDL-C	High-Density Lipoprotein Cholesterol
IL-10	Interleukin 10
LDL-C	Low-Density Lipoprotein Cholesterol
MACEs	Major Adverse Cardiovascular Events
MPP	Million Persons Project
O-GlcNA	O-GlcNAcylation
OGT	O-GlcNAc Transferase
PEACE	Patient-Centered Evaluative Assessment of Cardiac Events
PEACE-MPP	Patient-centered Evaluative Assessment of Cardiac Events Million Persons Project
PLIN1	Lipid-Droplet-Related Perilipin-1
PTM	Post-Translational Modification
SBP	Systolic Blood Pressure
SYNTAX	SYNergy Between PCI with TAXUS™ and Cardiac Surgery
TIMI	Thrombolysis in Myocardial Infarction
TSP	Thrombospondin
UDP-GlcNAc	Uridine diphosphate N-acetylglucosamine
WHO	World Health Organization

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Author contributions

Fang Ding and Wei Yu carried out the studies, participated in collecting data, and drafted the manuscript. Shiyun Hu, Jing Yan, and Fang Ding performed the statistical analysis and participated in its design. Xiaoling Xu and Jianlin Shao participated in the acquisition, analysis, or interpretation of data and drafted the manuscript. All authors read and approved of the final manuscript.

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Data availability
All data generated or analysed during this study are included in this article.

Declarations

Ethics approval and consent to participate
This study was approved by the Medical Ethics Committee of Zhejiang Hospital (2018 11 K), and the requirement for informed consent was waived by the Medical Ethics Committee of Zhejiang Hospital because of the study's retrospective nature. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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