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Predictive value of coronary artery calcium score in cardiovascular disease

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1. ABSTRACT

We investigated coronary heart disease (CHD) and cardiovascular disease (CVD) event rates in a diverse population with a coronary artery calcium score (CACS) of 0 and the role of CACS in the detection of subclinical noncalcified atherosclerotic plaque. A total of 15,884 participants in five studies were included in this meta-analysis. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated. The results showed that CHD incidence significantly increased with increased CACS (HR=0.05, 95% CI 0.03–0.06, Z=5.82, P=0.002). The CHD rate was low and further increased with CACS of 101–300. With CACS >300, the CHD rate was highest. Similarly, CVD rate was low with CACS of 0, increased with CACS of 1–100 (HR=0.03, 95% CI 0.01–0.06, Z=1.66, P=0.096), and further increased with CACS of 101–300. With CACS >300, the CVD rate was highest. Clinical evidence indicated that the higher the CACS, the higher the CHD and CVD rates, while the CVD rate does not always decreased compared with CHD rate with the same CACS, especially with CACS of 0.

2. INTRODUCTION

The coronary artery calcium score (CACS), detected by computed tomography (CT), has been

applied for more than 20 years to provide an early diagnosis for coronary artery disease (CAD) in clinical routine practice and is useful in predicting future cardiac events (1-5) and subclinical atherosclerosis (2). CACS, as assessed by non-contrast coronary CT angiography, which identifies ruptured and vulnerable plaques with good specificity (13,23), is an excellent overall measure of coronary atherosclerotic burden that is generally highly incremental over traditional risk factors (25) and clinical risk prediction schemes (26, 27). Early detection of vulnerable plaques is important in the prevention and treatment of coronary heart disease (CHD) (7). Traditional results have shown that CACS is viewed as a marker to primarily determine CHD risk, given that the location of the calcification is in the coronary arterial bed. CACS correlates with the presence of coronary artery disease and, because of the dynamic nature of atherosclerosis, serial alterations in CACS appears to be consisent with progression of atherosclerosis, and in providing additional prognostic value (1, 6,12,22-24).

Among all negative risk markers, a CACS of 0 was the strongest marker for CVD. Net reclassification improvement analyses yielded similar findings, with CACS of 0 resulting in the largest, most accurate downward risk reclassification (10). Noncalcified plaque was detected by cardiac CT angiography (CCTA) with a varying extent and severity in individuals with a CACS score of 0. Therefore, we investigated the CHD and CVD event rates in a diverse population with a CACS of 0 and the examined the role of CACS in the detection of subclinical noncalcified atherosclerotic plaques. A CACS of 0 is associated with an extremely low but non-zero 10-year risk for cardiac events (14,15,33). While assessement by CACS would allow improved risk stratification, CHD and CVD event rates in a diverse population with a CACS of 0 and other scores remain unclear. To address this research gap, we conducted a systematic review and meta-analysis of published reports to examine the predictive value of CACS in CVD and CHD.

3. METHODS

3.1. Search strategy

A literature search was performed for English articles in the PubMed (from January 1980 to December 2017), EMBASE (from January 1988 to December 2017), and Cochrane (from January 1995 to December 2017) databases. Articles pertaining to CACS in patients with CHD or CVD were identified.Key search words included the following: CACS, CVD, and CHD. Data extraction was performed independently using a predefined form (Table 1).

3.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) study population diagnosed using only the CACS detected by CT; (2) study design of RCT or non-RCT; and (3) absence of interventions. The exclusion criteria were as follows: (1) presence of adjusted risk factors adjusted and (2) presence of ΔCACS change in CAC/year.

3.3. Subjects

CACS was defined by non-contrast CCTA or electron-beam CT. A total of five studies that defined CACS using the criteria of average Agatston scores from two scans performed upon examination and adjusted with a standard calcium phantom (scanned with the participant) to calibrate X-ray attenuation between measurements performed on different machines were included in the study.

3.4. Assessment scale

Two investigators (S Liu and L Zheng) independently performed quality assessment of all included articles, using the Cochrane Collaboration tool (8, 9). In case of discrepancies, a third investigator (K Sun) participated in the discussion to establish the final assessment. The CASP Collaboration tool assesses the risk of bias in the following domains: selection, performance, detection, attrition, reporting, and others. Each domain was assigned a score.

3.5. Search results

Finally, a total of 488 studies were retrieved in the primary screening and search, 464 of which were duplicates. Based on our criteria, five studies were eligible for full-text review. The exclusion process of 19 articles is shown in Figure 1. One

Table 1. Baseline characteristics of the included studies

Study			Duration of	Study	Number of	Study	Study	Study	Study
year	author	country	Follow up	CACS (Agatston Units)	participants	CHD	CVD	age	Group
2014	Michael G. Silverman (20)	USA	7.1 ± 1.0	0	3349	0.013	—	62±10.0	1
2014	Michael G. Silverman (20)	USA	7.1 ± 1.0	1-100	1774	0.0479	—	62±10.0	2
2014	Michael G. Silverman (20)	USA	7.1 ± 1.0	101-300	747	0.0977	—	62±10.0	3
2014	Michael G. Silverman (20)	USA	7.1 ± 1.0	＞300	828	0.1654	—	62±10.0	4
2011	Michael J. Blaha (29)	six field centers	5.8	0	444	0.0048	0.0212	66.5±9.0	1
2011	Michael J. Blaha (29)	six field centers	5.8	1-100	267	0.0279	0.0486	66.5±9.0	2
2016	Udo Hoffmann (21)	American	8	1-100	882	0.0146	0.0136	50±10	2
2016	Udo Hoffmann (21)	American	8	101-300	270	0.0463	0.0373	50±10	3
2016	Udo Hoffmann (21)	American	8	>300	259	0.0963	0.0427	50±10	4
2014	Ashleigh O Gibson (28)	6 US communities	9.5	0	3399	—	0.02	67.9 ± 9.6	1
2014	Ashleigh O Gibson (28)	6 US communities	9.5	1-100	1786	—	0.0375	67.9 ± 9.6	2
2014	Ashleigh O Gibson (28)	6 US communities	9.5	101-400	923	—	0.0563	67.9 ± 9.6	3
2014	Ashleigh O Gibson (28)	6 US communities	9.5	>400	671	—	0.0685	67.9 ± 9.6	4
2016	Parag H. Joshi (5)	6 field centers	10.4	0	912	0.0087	—	58.6	1
2016	Parag H. Joshi (5)	6 field centers	10.4	1-100	296	0.0236	—	58.6	2
2016	Parag H. Joshi (5)	6 field centers	10.4	>100	183	0.0983	—	58.6	

Michael J. Blaha included six study centers (Baltimore; Chicago; Forsyth County, North Carolina; Los Angeles; New York; and St. Paul, Minnesota); Matthew J. Budoff included six US communities (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; Los Angeles County, CA); Parag H. Joshi included six study centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). CCLS, Cooper Center Longitudinal Study

article on type 2 diabetes (16), one on hard ASCVD events and stratified CHD (14), one on ΔCACS change in CAC/year (17), and one on aspirin use (18) were excluded.

3.6. Study quality

The detailed quality features of the studies are shown in Table 2 (19). The maximum score was 10. The studies were assessed for clear research question, manner of answering the question, control group, exposure factors, association factors, result accuracy, and applicability of results.

3.7. Statistical methods

The primary risk factor for plaque in this meta-analysis was mean change in CACS. Mean

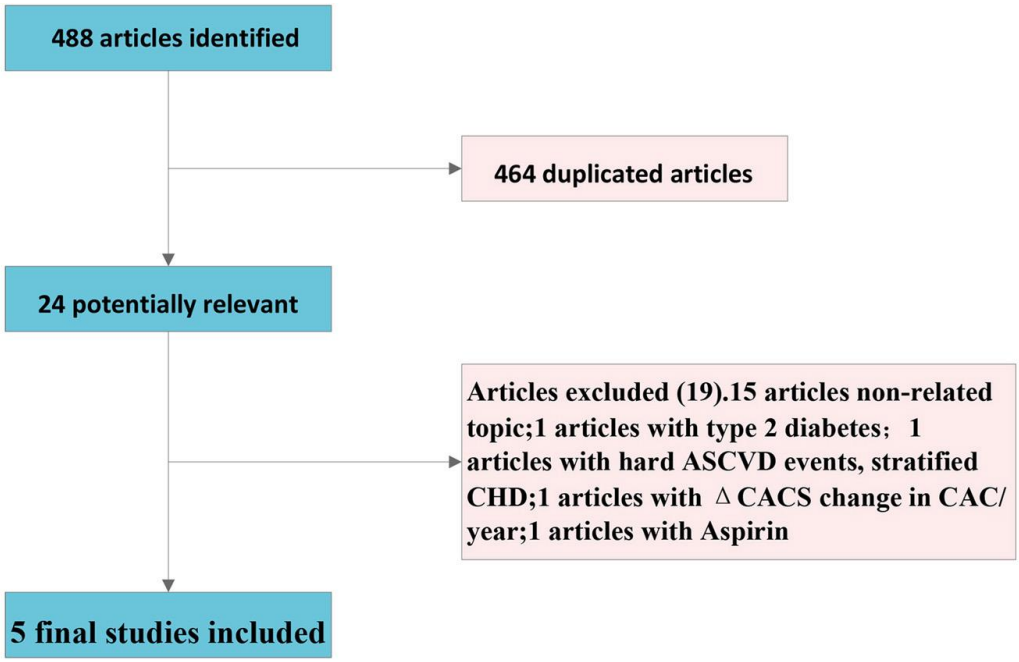

Figure 1. Flow diagram of the search strategy

changes in CACS between baseline and follow-up visits were determined. Heterogeneity among the included studies was analyzed using the I^2 index as follows: I^2 = ((Q–df)/Q)×100%, where Q is the χ^2 heterogeneity statistic and differs in degrees of freedom. A meta-regression analysis was performed to explore associations of CACS with cardiovascular events, such as CHD and CVD. A random effects model was used to estimate the overall mean changes. I^2 indicated substantial heterogeneity (statistically significant heterogeneity). A forest plot was generated to explore the associations of CACS and mean risk rates in the CVD and CHD groups. Publication bias was examined using a funnel plot (Begg's test). All statistical analyses were conducted using the statistical software package Stata 12.0.m (StataCorp, College Station, TX, USA).

4. RESULTS

4.1. Baseline characteristics of the participants

There were 259–3349 participants in various studies. A total of five studies reported mean changes in Agatston CACS only. The remaining six studies reported the pooled effect of Agatston CACS (Table 1). The follow-up duration ranged from 5.8 to 10.4 years for the long term (group 1, score=0; group 2, 1≤score≤100; group 3, 101≤score≤300; group 4, score >300).

4.2. Quality assessment

The CASP tool that was used in assessing risk of bias in randomized trials is shown in Table 3, which included clear question, manner of answering the question, control group, exposure factor, mingle factor, result accuracy, and applicability of the results. Detailed information on the quality assessment using the CASP tool is shown in Table 3. Three included studies (5,28–29) have more than one applicable results classified as having a low risk of bias, whereas two studies by Silverman (20) and Hoffmann (21) were deemed unclear in the "exposure factor" and other bias domains. In fact, all included studies were open-label trials, in which score bias was only defined as "score >100." Silverman (20) and Hoffmann (21) had allocation concealment only in one city.

Table 2. Meta-regression analysis for CACS prediction of CHD or CVD incidence rate

Study	*P* value	
Variables	**CHD**	**CVD**
Score	0.001	0.023
Number of patients	0.597	0.382
Year	0.811	0.842
Age	0.887	0.561

Table 3. CASP tool for assessing risk of bias in randomized trials

Study		Bias of CASP						
year	**author**	**Clear question**	**Answer the question**	**Control group**	**Exposure factor**	**Mingle factor**	**Results accuracy**	**Applicable results**
2014	Michael G. Silverman (20)	9	9	9	9	9	9	7
2011	Michael J. Blaha (29)	9	7	8	8	7	8	8
2016	Udo Hoffmann (21)	9	8	8	8	8	8	7
2014	Ashleigh O Gibson (28)	9	9	8	9	9	9	8
2016	Parag H. Joshi (5)	9	7	7	7	8	9	8

A meta-regression analysis was conducted to examine the reasons for heterogeneity. Regression results revealed that CACS was the main reason for heterogeneity. Heterogeneity remained despite the generation of four subgroups for Agatston CACS, with overall I^2 of 99.9.% (p<0.0.5). The score was included in the meta-regression analysis, and heterogeneity was found (p=0.0.01), while the number of enrolled patient (p=0.5.97), publication year (p=0.8.11), and patient age (p=0.8.87) showed no significant differences (Table 2).

We divided the patients into four groups according to CACS. Random effects models were used to determine total and subgroup effects. The subgroup analysis indicated that considerable heterogeneity existed between the CACS groups. The subgroup analysis of patients indicated that CACS markedly increased with CHD and CVD incidence rates.

A forest plot was generated according to CACS predicting the CHD or CVD rate (Figure 2). The analysis revealed that CHD incidence significantly increased with increased CACS (HR=0.0.5, 95% CI 0.0.3–0.0.6, Z=5.8.2, P=0.0.02). The CHD rate was low with CACS of 0 (HR=0.0.1, 95% CI 0.0.0–0.0.1, Z=3.7.7, P=0.0.01), increased with CACS ranging from 1 to 100 (HR=0.0.3, 95% CI 0.0.1–0.0.5, Z=3.0.4, P=0.0.02), and further increased with CACS ranging from 101 to 300 (HR=0.0.7, 95% CI 0.0.2-0.1.2, Z=2.8.2, P=0.0.05). With CACS >300, the CHD rate was highest (HR=0.1.3, 95% CI 0.0.6–0.2.0, Z=3.8.3, P=0.0.01). Similarly, CVD incidence increased with increased CACS (HR=0.0.3, 95% CI 0.0.2–0.0.4, Z=6.1.2, P=0.0.01). The CVD rate was low (HR=0.0.2, 95% CI 0.0.2–0.0.2, Z=8.8.9, P=0.0.01) with CACS of 0, increased with CACS of 1–100 (HR=0.0.3, 95% CI 0.0.1–0.0.6, Z=1.6.6, P=0.0.96), and further increased with CACS of 101–300 (HR=.04, 95% CI 0.0.3–0.0.5, Z=8.9.6, P=0.0.01). With CACS >300, the CVD rate was highest (HR=0.0.6, 95% CI 0.0.3–0.0.8, Z=4.4.2, P=0.0.01). Publication bias was examined using a funnel plot (Begg's test) (Figure 3). The funnel plot for CHD rate was biased (Kendall's score=35, Z=2.72, P=0.0.08), but that for CVD rate was not (Kendall's score=12, Z=1.4.8, P=0.1.74).

5. DISCUSSION

The current meta-analysis calculated the CHD and CVD event rate at the same CACS was not clear, especially when CACS at zreo.(erroneous.

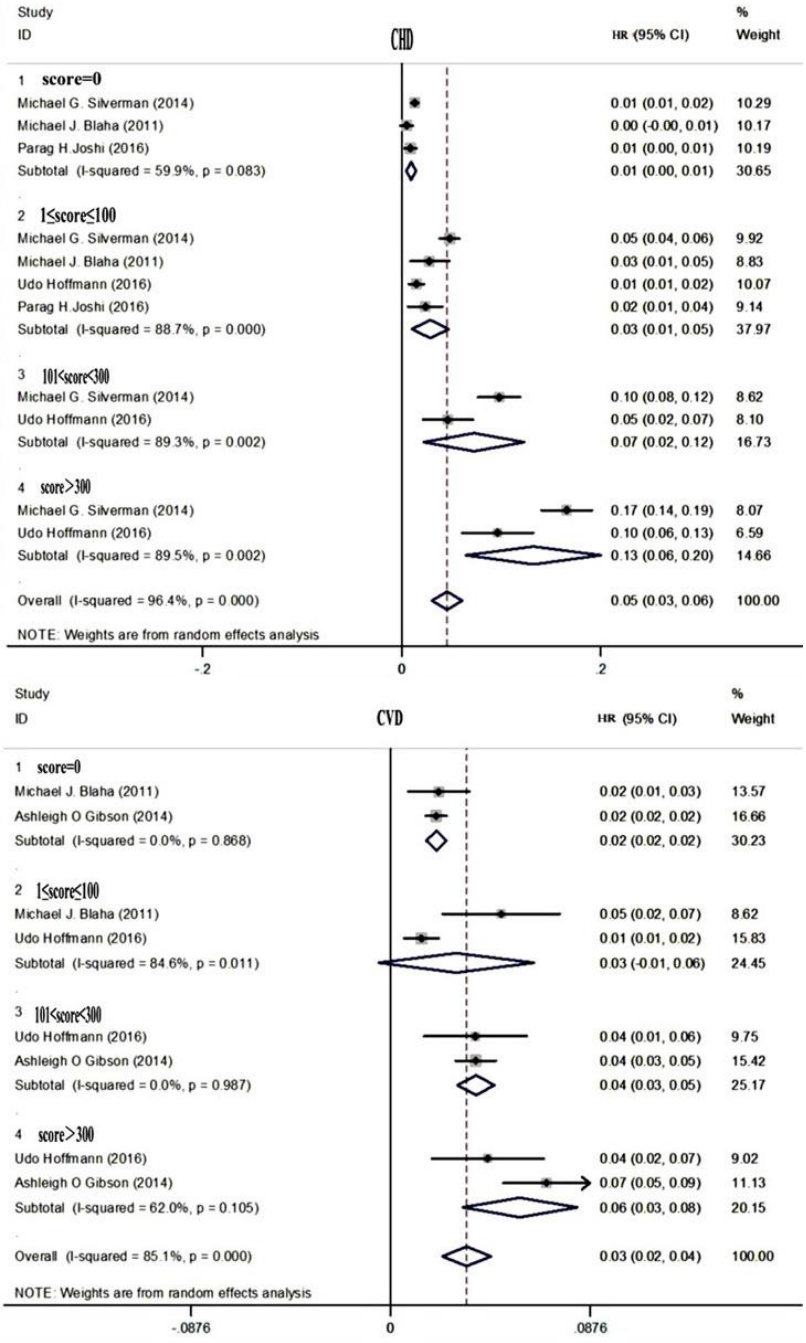

Figure 2. Forest plot according to CACS predicting the CHD or CVD rate (group 1, score=0; group 2, 1≤score≤100; group 3, 101≤score≤300; group 4, score >300).

Meaning not clear). The meta-regression analysis demonstrated significant heterogeneity among those included in the studies. Risk prediction equations are recommended for clinical use to select the best candidates for preventive therapies (15). The impact of CACS on CHD events is high in individuals at

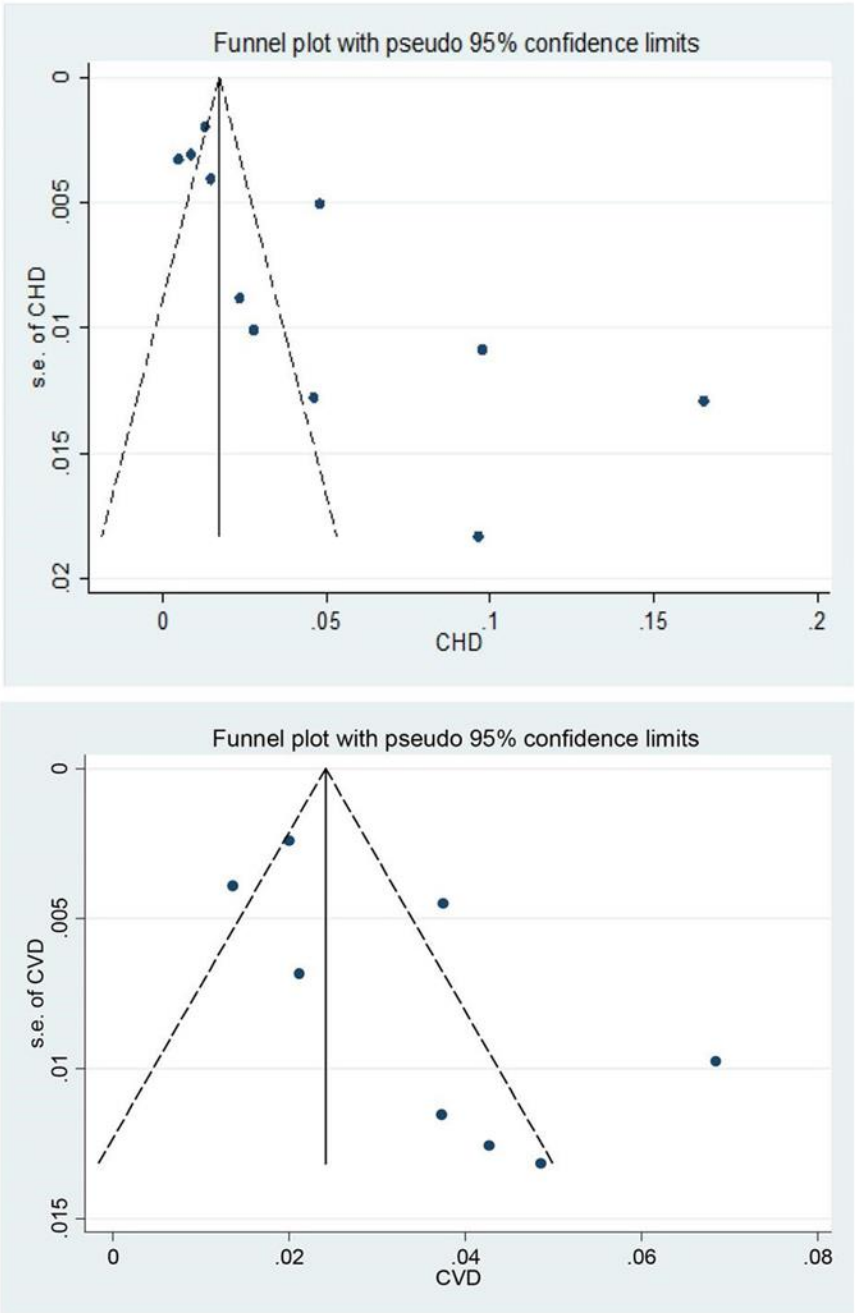

Figure 3. Funnel plots for CACS significantly increases with the incidence rate of CHD or CVD. CHD, Kendall's score=35, Z=2,72, *P*=0.0.08; CVD, Kendall's score=12, Z=1.4.8, *P*=0.1.74.

extremes of traditional risk factor burden (20). Moreover, studies have assessed risk factors and CACS changes (14, 17, 24). The meta-regression analysis demonstrated significant heterogeneity among all included studies. However, the clinical heterogeneity among articles was available as the effect of each study had the same direction. The subgroup analysis and random effects models were

used to examine the pooled effect based on different CACS groups.

Traditional results showed that the CACS has been viewed as a marker to primarily determine the CHD risk given that the location of the calcification is in the coronary arterial bed and, because of the dynamic nature of atherosclerosis, serial alterations in CACS might reflect progression of atherosclerosis, providing an additional prognostic value (1, 22-24). CACS, determined by non-contrast CT (23), is an excellent overall measure of coronary atherosclerotic burden and provides information on plaque prognosis (13) that is generally highly incremental over traditional risk factors (25) and clinical risk prediction schemes (26, 27). A CHD event is defined as myocardial infarction, death from CHD, resuscitated from cardiac arrest or definite angina, and revascularization in case of adjudicated preceding or concurrent angina. A CVD event is defined as a CHD event or stroke (not transient ischemic attack), cardiovascular death, or other deaths related to atherosclerosis (2, 21). CACS is a direct measurement of atherosclerotic plaque components in the coronary arteries and a potent predictive factor of future CHD or CVD events (15, 17, 21). Therefore, the current results showed that the higher the CACS, the higher the CHD or CVD rate.

However, Blaha (29) reported higher CVD rate than CHD rate for the same scores, while Hoffmann (21) obtained lower CVD rates as compared with the CHD rate for the same scores. The current meta-analysis showed a higher CVD rate than that of CHD rate with CACS of 0, while with CACS ≥101, a higher CHD rate than CVD rate was obtained. Moreover, a 1≤CACS≤100 yielded similar CHD and CVD rates. These findings indicated that plaque or coronary artery calcium burden may impact CHD events in individuals at extreme traditional risk (26). One possible explanation for these findings could be that, due to the long follow-up period, participants had CVD events more than had CHD events with a CACS of 0 (33). Furthermore, some studies were conducted only on one location, whereas others were conducted on six fields, resulting in difficulty in calculating the standard value of exercise quantity.

To the best of our knowledge, this is the first meta-analysis assessing the predictive value of CACS in predicting future CHD or CVD events. The subgroup analysis indicated that considerable heterogeneity existed between the CACS groups. The subgroup analysis of patients indicated that CACS markedly increased with CHD and CVD incidence rates. When the score was included in the meta-progression analysis to assess heterogeneity (*P*=0.0.01), the number of enrolled patients (*p*=0.5.97), publication year (*p*=0.8.11), and patient age (*p*=0.8.87) showed no significant differences. Therefore, the patients were divided into four groups according to their scores. The present study focused on associations of CACS with CHD and CVD events. The participants were divided into four groups based on baseline CACS (CAC=0, 1–100, 100–300, and >300). The study by Joshi et al. (5) only showed “score >100” and was excluded. Meanwhile, Gibson et al. (28) reported a score of “1–400,” and the patients were assigned to three groups; patients with a score >400 were included in group 4.

The strength of this study was that the majority of included studies had long-term follow-up. The present analysis also had several limitations, as the studies included were limited to articles published in English. Moreover, large sample sizes and various geographic locations contributed to a diverse and comprehensive set of data. Furthermore, two studies showed heterogeneity; despite the subgroup analysis, heterogeneity was mostly statistically significant. Therefore, further rigorous studies are required to confirm the current findings. Moreover, combined HR for CHD and CVD was unsatisfactory. Meanwhile, subgroups were based on large intervals, which may increase heterogeneity in our analysis. Finally, the funnel plot for CHD rate was biased (Kendall’s score=35, Z=2,72, *P*=0.0.08). Agatston score is a semi-automated tool to determine a score based on the extent of coronary artery calcification detected by unenhanced low-dose CT, which is routinely performed in patients undergoing cardiac CT. The predictive value of CACS is consistently superior to that of the carotid plaque score or carotid intima-media thickness for all CHD and CVD events (30, 31). CACS predicts CHD events and can be serially measured to evaluate atherosclerosis progression (5). It provides a noninvasive direct

measurement of coronary atherosclerosis and remains significant, also according to previous guidelines (32).

The presence of coronary noncalcified plaque in participants with CACS of 0 leads to a higher risk of CVD events than of CHD events. More studies are needed to assess the value of noncalcified plaque in patients with a CACS of 0.

6. ACKNOWLEDGMENTS

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Abbreviations: CHD: coronary heart disease; CVD: cardiovascular disease; cardiovascular disease: coronary artery calcium score; HRs: Hazard ratios; CT: Computed tomography, CCTA: Coronary CT angiography, Review

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