Deep-learning-based cardiovascular risk stratification using coronary artery calcium scores predicted from retinal photographs

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Summary

Background Coronary artery calcium (CAC) score is a clinically validated marker of cardiovascular disease risk. We developed and validated a novel cardiovascular risk stratification system based on deep-learning-predicted CAC from retinal photographs.

Methods We used 216 152 retinal photographs from five datasets from South Korea, Singapore, and the UK to train and validate the algorithms. First, using one dataset from a South Korean health-screening centre, we trained a deep-learning algorithm to predict the probability of the presence of CAC (ie, deep-learning retinal CAC score, RetiCAC). We stratified RetiCAC scores into tertiles and used Cox proportional hazards models to evaluate the ability of RetiCAC to predict cardiovascular events based on external test sets from South Korea, Singapore, and the UK Biobank. We evaluated the incremental values of RetiCAC when added to the Pooled Cohort Equation (PCE) for participants in the UK Biobank.

Findings RetiCAC outperformed all single clinical parameter models in predicting the presence of CAC (area under the receiver operating characteristic curve of 0·742, 95% CI 0·732–0·753). Among the 527 participants in the South Korean clinical cohort, 33 (6·3%) had cardiovascular events during the 5-year follow-up. When compared with the current CAC risk stratification (0, >0–100, and >100), the three-strata RetiCAC showed comparable prognostic performance with a concordance index of 0·71. In the Singapore population-based cohort (n=8551), 310 (3·6%) participants had fatal cardiovascular events over 10 years, and the three-strata RetiCAC was significantly associated with increased risk of fatal cardiovascular events (hazard ratio [HR] trend 1·33, 95% CI 1·04–1·71). In the UK Biobank (n=47 679), 337 (0·7%) participants had fatal cardiovascular events over 10 years. When added to the PCE, the three-strata RetiCAC improved cardiovascular risk stratification in the intermediate-risk group (HR trend 1·28, 95% CI 1·07–1·54) and borderline-risk group (1·62, 1·04–2·54), and the continuous net reclassification index was 0·261 (95% CI 0·124–0·364).

Interpretation A deep learning and retinal photograph-derived CAC score is comparable to CT scan-measured CAC in predicting cardiovascular events, and improves on current risk stratification approaches for cardiovascular disease events. These data suggest retinal photograph-based deep learning has the potential to be used as an alternative measure of CAC, especially in low-resource settings.

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Introduction

Cardiovascular disease is the leading cause of death worldwide.[1] Coronary artery calcium (CAC) is a preclinical marker of atherosclerosis and is strongly associated with risk of clinical cardiovascular disease.[2] Measurement of CAC scores has increasingly been used for stratification of cardiovascular disease risk, in conjunction with clinical risk prediction models in international guidelines.[3,4] The American College of Cardiology/American Heart Association (ACC/AHA) guidelines[3,4] recommend the use of the Pooled Cohort Equation (PCE) to stratify people at risk of cardiovascular disease and determine who should be given statin therapy. However, for patients classified in the intermediate-risk group based on the PCE, the clinician–patient risk discussion can include risk-enhancing factors (eg, family history or CAC score). CAC score has been recommended as an additional test to refine risk estimates and improve selection for statin treatment.[3,4] However, current measurement of CAC scores requires ready access to CT scans, which carries radiation risk.

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Research in context

Evidence before this study

Current guidelines such as the American College of Cardiology/American Heart Association guideline use the Pooled Cohort Equation (PCE) to stratify people at risk of cardiovascular disease to determine commencement of statin therapy. For the intermediate-risk group, guidelines recommend measuring coronary artery calcium (CAC) to assist in the decision of statin therapy. We derived a deep learning-based CAC score predicted from retinal photographs (RetiCAC) and used this new RetiCAC score for cardiovascular risk stratification. Our search strategy consisted of studies that applied deep learning on retinal photographs for the prediction of cardiovascular events as of Sept 13, 2020. We combined the search terms artificial intelligence ("deep learning" or "machine learning"), retinal image ("fundus" or "retina"), and "coronary artery calcium". We found only one study using deep learning to predict high CAC scores based on retinal photographs, but without demonstration of external validation.

Added value of this study

We developed RetiCAC to predict the presence of CT scan-measured CAC. Based on RetiCAC, a new three-tier cardiovascular disease risk stratification system was developed, which showed comparable performance as current CT scan, and incremental prognostic performance over PCE in borderline-risk and intermediate-risk groups. The value added by this work lies in the demonstration of a retinal photograph-based deep learning algorithm in predicting future major health events (ie, cardiovascular disease events and mortality) with external validation. To our knowledge, this is also the first study that compared the performance of a retinal photograph-based deep learning algorithm with established clinical guideline standard, in predicting major cardiovascular events.

Implications of all the available evidence

With deep learning, retinal photographs can provide an estimate of CAC score, and could be used as a surrogate marker for cardiovascular risk stratification, which was compatible with cardiac CT scan in predicting cardiovascular disease events. Taken together, our findings suggest that retinal photography may be adopted as a more cost-effective method as compared with cardiac CT and non-radiation imaging modality for cardiovascular risk stratification.

Retinal photographs provide information about human vasculature and insights into cardiovascular health.[5] Large population studies have shown that overt retinal vascular damage (eg, signs of retinopathy such as microaneurysms and retinal haemorrhages) and more subtle changes (eg, retinal arteriolar narrowing) are markers of subclinical cardiovascular disease (eg, carotid artery stenosis), and can predict major cardiovascular disease events and mortality.[6–10] The recent application of artificial intelligence through deep-learning algorithms has suggested that retinal photographs can provide estimates on traditional cardiovascular disease risk factors, such as age, sex, and blood pressure,[11,12] and can predict cardiovascular disease events with similar accuracy to a traditional cardiovascular disease risk calculator.[12]

We have extended this concept and hypothesise that retinal photograph-based deep learning can also predict CAC score, and this retinal-predicted score can also be used as a risk stratification tool for cardiovascular events. This hypothesis is relevant given that CAC is recommended[3,4] as an additional test to help clinicians to better determine statin indication. Here, we developed a deep-learning algorithm to predict the probability of the presence of CAC based on retinal photographs (termed the deep-learning retinal CAC score, RetiCAC). Secondly, based on the RetiCAC, we proposed a new simplified cardiovascular disease risk stratification system and validated its performance in data from three longitudinal studies from South Korea, Singapore, and the UK Biobank. Lastly, in the UK Biobank, we assessed whether RetiCAC could be used for cardiovascular disease risk discrimination similar to cardiac CT measured CAC, in line with current ACC/AHA guidelines, specifically among people in the PCE borderline-risk and intermediate-risk groups.

Methods

Study design and population

We used clinical data and retinal photographs from five independent datasets or studies, including two datasets from two health-screening centres in South Korea; Cardiovascular and Metabolic Disease Etiology Research Center-High Risk (CMERC-HI), a prospective clinical cohort in South Korea; the Singapore Epidemiology of Eye Diseases (SEED) study, a prospective population-based cohort in Singapore; and the UK Biobank, a prospective population-based cohort in the UK.

First, we extracted data from individuals who visited the health-screening centre affiliated with Severance Hospital, South Korea (screening centre 1; developmental and internal test set). We then extracted data from individuals who visited a health-screening centre affiliated with the Philip Medical Centre, South Korea (screening centre 2; external test set 1). For comparison between the RetiCAC and CAC score for risk stratification in clinical settings, we used clinical data from a longitudinal study, the CMERC-HI cohort (ClinicalTrials.gov, NCT02003781),[13] which targeted patients with a high cardiovascular disease risk (external test set 2). All examinations, including cardiac CT scans and retinal photography, were done on the same visit day in datasets from South Korea. In

addition, we included the SEED cohort to determine the association between the RetiCAC score and incidence of cardiovascular disease events in an Asian general population comprising Chinese, Malay, and Indian people.[14] Lastly, we used the UK Biobank data to evaluate the added value of our proposed RetiCAC score on the PCE[3,4] in cardiovascular disease risk stratification.

Detailed information on the retinal cameras, CT scanning system, and measurements of clinical outcomes used is provided in the appendix (pp 1–2). The numbers of patients excluded and included from the study populations are shown in the appendix (pp 3–4, 9). We included all participants to maximise the number of pairs of retinal photographs and cardiac CT scans for deep-learning model development. We then excluded missing data in four well established risk factors (smoking, hypertension, diabetes, and dyslipidaemia) in screening centre 1 for model evaluation (denoted as subset). In the UK Biobank, participants who were taking statins,[15] and had cardiovascular disease at baseline were excluded.

This study was approved by the institutional review board of Severance Hospital, Yonsei University, Seoul, South Korea (4-2013-0581, 4-2018-0262, 4-2019-1259), and adhered to the tenets of the Declaration of Helsinki. Written, informed consent was obtained from the participants in the clinical cohort study and population-based cohort studies.

Definition of the presence of CAC

We defined a CAC score of zero as absence of CAC, and more than zero as presence of CAC. The selection of this cutoff was supported by a series of studies that found a low cardiovascular disease risk among individuals with a CAC score of zero.[16,17]

Deep-learning algorithm for predicting the presence of CAC

Details regarding model development and visualisation techniques (ie, saliency maps) are provided in the appendix (pp 5–6). In model development, CAC was the main outcome as a binary variable, and the model inputs comprised of retinal photographs. We developed a deep-learning algorithm using retinal photographs to predict the probability of the presence of CAC (ie, CAC scores >0), which we referred to as the RetiCAC score. To generate the saliency maps, we used guided backpropagation,[18] and aggregated analysis was done.

Definition of cardiovascular disease events

In SEED, incident cardiovascular disease events were obtained by linking with Singapore's National Registry of Disease Office.[19] In the UK Biobank, we used hospitalisation and mortality data provided by the National Health Service (NHS) registers.[20] In both SEED and UK Biobank, the primary outcome was incident fatal cardiovascular disease events, defined based on the European Systematic COronary Risk Evaluation (SCORE) clinical guidelines[21] (International Classification of Diseases [ICD]-10 codes, I10–15, I44–51, I20–25, and I61–73; hereafter SCORE cardiovascular disease events).[20,22] The secondary outcome was incident atherosclerotic cardiovascular disease (ASCVD) events, defined in accordance with the ACC/AHA guidelines[3] (hereafter, referred to as ACC/AHA ASCVD events) including fatal ASCVD events (ICD-10 codes I20–25, I60–64) and non-fatal ASCVD events (hospitalisation due to ICD-10 codes I21, I22, I60–64).[20]

See Online for appendix

In CMERC-HI, we defined cardiovascular disease events as any of incident cardiovascular disease including heart failure, stroke, myocardial infarction, or all-cause mortality (detailed definitions can be found in the appendix p 7). In CMERC-HI, other-cause mortality was also included in the evaluated outcome, because the non-fatal and fatal cardiovascular disease events were relatively few due to a short follow-up of 5 years.

New cardiovascular disease risk stratification system

The RetiCAC score was defined based on a probability score derived from our deep-learning algorithm of binary classification (absence *vs* presence of CAC). The probability scores ranged from zero to one, with a high value indicating a high probability of the presence of CAC. The distribution of the estimated RetiCAC scores is provided in the appendix (p 10). We proposed a new cardiovascular disease risk stratification system based on the tertiles of RetiCAC scores in CMERC-HI (1st tertile ≥0 to <0·3093, low risk; 2nd tertile ≥0·3093 to ≤0·4074, moderate risk; and 3rd tertile >0·4074 to ≤1, high risk). We then compared the performance of our proposed RetiCAC system in predicting cardiovascular disease events to that based on three-strata risk stratification according to cardiac CT-measured CAC scores (0, >0–100, and >100).[3] We also used these proposed cutoff values to further stratify the cardiovascular disease risk in the SEED and UK Biobank participants.

Calculation of the PCE in the UK Biobank

We estimated cardiovascular disease risk according to the PCE, following the ACC/AHA guidelines.[3] In our primary analysis, we included only White participants in the UK Biobank, and estimated their 10-year ASCVD risk according to the PCE, because most (92%) of the UK Biobank participants were White and the equation was only validated for non-Hispanic Black people and non-Hispanic White people.[3] The distribution of the PCE estimates is provided in the appendix (p 10).

Statistical analysis

Analyses were done using p less than 0·05 as the significance level, and using Python 3.7 for deep-learning algorithm development, Stata/MP version 14.0 for survival analysis, and R version 3.4.4 for estimation of

	Subset from screening centre 1 (internal test set)	Screening centre 2 (external test set 1)	CMERC-HI (external test set 2)	SEED	UK Biobank
Participants	2536	8707	527	8551	47 679
Examinations	2795	9460	527	8551	47 679
Retinal photographs	5590	18 920	1054	17 102*	95 358
CAC					
Median	0·0 (0·0–10·0)	0·0 (0·0–2·8)	16·3 (0·0–170·6)	NA	NA
0	1873 (67·0%)	6789 (71·8%)	217 (41·2%)	NA	NA
>0	922 (33·0%)	2671 (28·2%)	310 (58·8%)	NA	NA
>100	286 (10·2%)	709 (7·5%)	165 (31·3%)	NA	NA
Clinical biomarkers					
Age, years	53·6 (7·0)	50·3 (7·5)	60·0 (11·7)	58·1 (10·2)	56·6 (8·2)
Sex					
Female	802 (38·0%)	2689 (36·4%)	246 (46·7%)	4472 (52·3%)	27 012 (56·7%)
Male	1734 (62·0%)	6018 (63·6%)	281 (53·3%)	4079 (47·7%)	20 667 (43·3%)
Systolic blood pressure, mm Hg	123·8 (14·8)	119·7 (13·5)	131·2 (15·4)	139·5 (21·8)	139·2 (19·6)
Diastolic blood pressure, mm Hg	78·4 (10·8)	73·0 (9·6)	78·6 (8·7)	78·6 (10·5)	81·5 (10·6)
Fasting glucose, mg/dL	101·4 (21·9)	104·0 (21·9)	108·8 (28·3)	120·6 (21·0)	90·9 (14·0)
Body-mass index, kg/m²	24·5 (3·4)	24·4 (3·3)	25·5 (3·6)	25·4 (4·7)	26·7 (4·5)
Hypertension	572 (20·5%)	NA	453 (86·0%)	5069 (59·3%)	24 375 (51·1%)
Diabetes	207 (7·4%)	NA	67 (12·7%)	2389 (27·9%)	691 (1·4%)
Dyslipidaemia	196 (7·0%)	NA	264 (50·1%)	3621 (42·4%)	14 494 (30·4%)
Current smoker	1264 (45·2%)	NA	234 (44·4%)	1354 (15·9%)	4058 (8·5%)
Cardiovascular disease events					
Total events	NA	NA	33 (6·3%)	NA	NA
Median follow-up, years	NA	NA	4·1 (3·8–4·5)	NA	NA
SCORE cardiovascular disease events†	NA	NA	NA	310 (3·6%)	337 (0·7%)
Median follow-up, years	NA	NA	NA	10·3 (8·7–12·7)	9·9 (9·8–10·1)
ACC/AHA ASCVD events‡	NA	NA	NA	992 (11·6%)	1184 (2·5%)
Median follow-up, years	NA	NA	NA	9·9 (8·3–11·5)	9·9 (9·7–10·0)

Data are n, n (%), mean (SD), or median (IQR). CMERC-HI=Cardiovascular and Metabolic Disease Etiology Research Center-High Risk Cohort. SEED=Singapore Epidemiology of Eye Diseases. CAC=coronary artery calcium. NA=not available. SCORE=Systematic COronary Risk Evaluation. ACC/AHA=American College of Cardiology/American Heart Association. ASCVD=atherosclerotic cardiovascular disease. *Estimated based on average number of photographs per person. †Primary outcome. ‡Secondary outcome.

Table 1: **Characteristics of the study population**

net reclassification index (NRI) using the R package survIDINRI.[23]

To evaluate the performance of the deep-learning algorithm, we calculated the area under the receiver operating characteristic curve (AUC) in the prediction of the presence of CAC.[24] The AUC of RetiCAC score was compared with that of age using Delong methods.[25] In addition, we used continuous NRI[23] to compare the performance of the multiparameter models with and without RetiCAC. To obtain the 95% CIs, we used the non-parametric bootstrap procedure with 2000 samples.

In CMERC-HI, each patient was followed up to 5 years from the date of baseline visit to the last follow-up date of Dec 31, 2018, or the date of the cardiovascular disease events. Cumulative incidence of cardiovascular events was evaluated across the three groups (low, moderate, and high risk) defined by the RetiCAC scores and across three groups stratified according to the cardiac CT-measured CAC scores (0, >0–100, and >100) using the Kaplan-Meier method, and Cox proportional hazards model to estimate the hazard ratios (HRs). Trends in HRs and p value for trend were examined by fitting a linear model for the tertile categories.

In both SEED and the UK Biobank, cumulative incidence of cardiovascular disease events was evaluated across the three risk groups (low, moderate, and high risk) defined by the RetiCAC score using Cox proportional hazard model. In SEED, hospitalisation and mortality data were available up to Dec 31, 2018, at the time of analysis and each participant was followed up to 14 years from the date of baseline visit. In the UK Biobank, hospitalisation and mortality data were available up to March 18, 2020, at the time of analysis and each participant was followed up to 10 years from the date of baseline visit. Risk-adjusted

	Internal test set	External test set 1	External test set 2
Single-parameter model			
LDL cholesterol	0·496 (0·472–0·519)	0·516 (0·503–0·530)	0·597 (0·547–0·646)
Total cholesterol	0·513 (0·490–0·537)	0·510 (0·497–0·523)	0·592 (0·543–0·642)
Dyslipidaemia	0·525 (0·514–0·536)	NA	0·562 (0·518–0·605)
Diabetes	0·540 (0·528–0·552)	NA	0·553 (0·527–0·580)
Triglyceride	0·562 (0·539–0·584)	0·595 (0·582–0·607)	0·512 (0·462–0·563)
HDL cholesterol	0·566 (0·544–0·588)	0·613 (0·600–0·625)	0·555 (0·506–0·605)
Diastolic blood pressure	0·575 (0·553–0·598)	0·582 (0·569–0·594)	0·498 (0·447–0·548)
Systolic blood pressure	0·577 (0·555–0·599)	0·613 (0·600–0·625)	0·588 (0·539–0·637)
Hypertension	0·589 (0·571–0·606)	NA	0·498 (0·468–0·528)
Current smoker	0·586 (0·566–0·605)	NA	0·533 (0·490–0·576)
Body-mass index	0·602 (0·581–0·624)	0·607 (0·595–0·619)	0·543 (0·492–0·594)
Sex	0·621 (0·604–0·639)	0·621 (0·611–0·630)	0·542 (0·499–0·585)
Glucose	0·628 (0·606–0·650)	0·637 (0·625–0·650)	0·563 (0·514–0·612)
Age	0·690 (0·669–0·710)	0·705 (0·693–0·716)	0·705 (0·660–0·749)
RetiCAC score*	0·731 (0·712–0·751)	0·742 (0·732–0·753)	0·729 (0·685–0·773)
Multiparameter model			
All risk factors†	0·769 (0·751–0·787)	0·782 (0·772–0·791)	0·725 (0·681–0·769)
All risk factors plus RetiCAC	0·769 (0·751–0·787)	0·784 (0·775–0·794)	0·749 (0·707–0·792)
NRI (95% CI)	0·227 (0·134–0·311)	0·267 (0·219–0·310)	0·321 (0·132–0·441)
NRI positive, NRI negative	0·082, 0·145	0·114, 0·153	0·058, 0·263

Data are AUC (95% CI), unless stated otherwise. The presence of CAC defined as a score of more than zero. NRI in individuals with abnormal CAC score (NRI positive) and individuals with zero CAC score (NRI negative) were provided (all p values were <0·0001). RetiCAC=deep-learning retinal coronary artery calcium. CAC=coronary artery calcium. AUC=area under the receiver operating characteristic curve. NA=data not available. NRI=net reclassification index. *Significant difference between age and RetiCAC models in internal test set and external test set 1 (p<0·0001), and non-significant difference in external test set 2 (p=0·249) based on DeLong's method. †All risk factors model included the 14 single parameters listed above. Non-significant difference between all risk factors and all risk factors plus RetiCAC models in internal test set and external test set 1 (p>0·05), and significant difference in external test set 2 (p=0·034) based on DeLong's method.

Table 2: **Performances of deep-learning RetiCAC score versus traditional clinical parameters in predicting individuals with the presence of CAC**

models included age, sex, hypertension, dyslipidaemia, diabetes, and smoking as covariates.

The incremental prognostic value of the RetiCAC over the PCE in the prediction of cardiovascular disease events was assessed using the Kaplan-Meier method, Harrell's C statistic,[25] and continuous NRI[23] in the borderline-risk and intermediate-risk groups in the UK Biobank. Cumulative incidence of cardiovascular disease events was evaluated across four risk groups stratified by the PCE (<5% [low risk]; 5% to <7·5% [borderline risk]; ≥7·5% to <20% [intermediate risk]; and ≥20% [high risk]), and the three groups (low, moderate, and high risk) according to the RetiCAC score.

For sensitivity analyses, in the UK Biobank, to account for the possibility of reverse causality, we did a landmark analysis in which we excluded participants who experienced events within the first 2 years of follow-up. We then repeated our analysis including individuals under statin treatment. In addition, we repeated our analysis including all participants (Black, Chinese, mixed or other ethnic backgrounds, south Asian, and White participants).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The clinical characteristics of study participants are provided in table 1. In CMERC-HI, the median baseline CAC score was 16·3 (IQR 0·0–170·6) and 33 (6·3%) of the 527 participants had cardiovascular disease events during the 5-year follow-up. In SEED, there were 310 (3·6%) SCORE cardiovascular disease events among 8551 participants. In the UK Biobank, there were 337 (0·7%) SCORE cardiovascular disease events among 47 679 participants. The characteristics of the entire dataset of screening centre 1 for development of deep-learning algorithm (appendix p 17) and those of the excluded participants (appendix p 18) are provided in the appendix.

Using the internal test set, the Spearman's rank correlation coefficient between RetiCAC and CT-measured CAC scores was 0·47 (p<0·0001, data not shown). The performance of RetiCAC in predicting presence of CAC is detailed in table 2. The RetiCAC score model showed superior performance with an AUC of 0·742 (95% CI 0·732–0·753), compared with single-parameter models, such as age (0·705, 0·693–0·716) and glucose (0·637, 0·625–0·650) in the external test set 1. However, after adding RetiCAC to the multiparameter model, there was little or no improvement in AUCs (p>0·05), and the

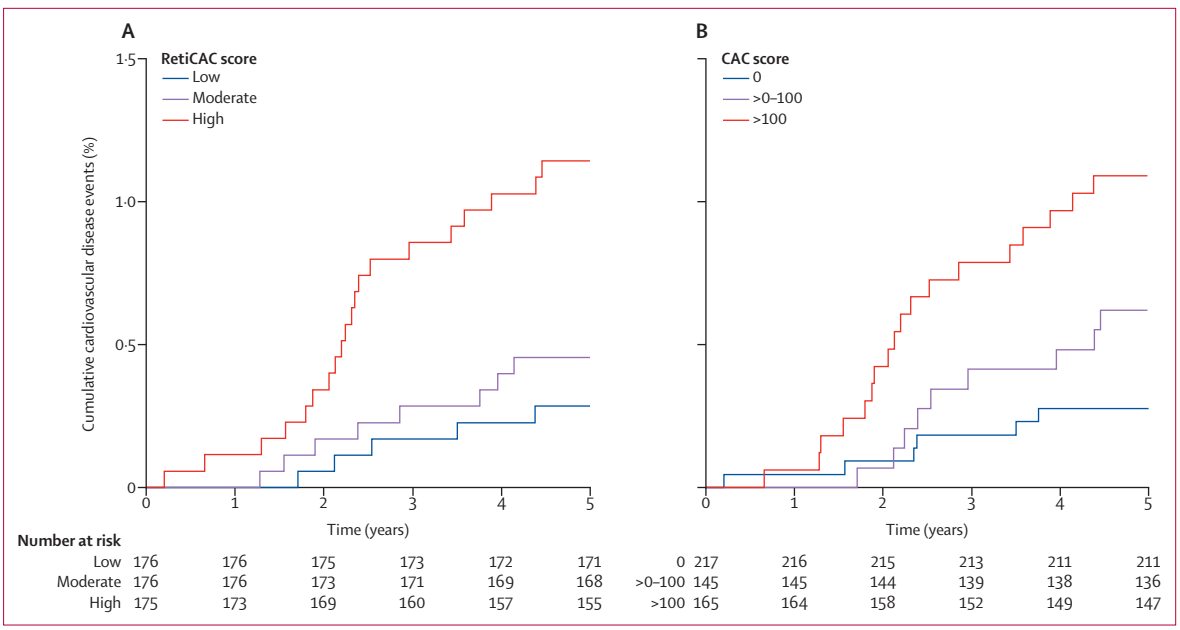


Figure 1: **Kaplan-Meier estimates for cumulative incidence of cardiovascular events in the CMERC-HI cohort**
(A) Cardiovascular disease event by RetiCAC score. (B) Cardiovascular disease event by CAC score. Cumulative event rates of cardiovascular disease events including incident heart failure, stroke, myocardial infarction, and all-cause mortality using the new three-strata risk stratification system of deep learning-based RetiCAC score (A), and CAC stratification (0, >0–100, and >100) (B) in the clinical cohort of CMERC-HI (n=527). CMERC-HI=Cardiovascular and Metabolic Disease Etiology Research Center-High Risk. CAC=coronary artery calcium. RetiCAC=deep-learning retinal coronary artery calcium.

continuous NRI was 0·267 (95% CI, 0·219–0·310) in external test set 1. Similar findings were observed in external test set 2. ROC and precision-recall curves (appendix p 11) and confusion matrices (appendix p 19) are presented in the appendix.

The saliency maps show that the deep-learning algorithm used features of blood vessels around the optic disc or arcade blood vessels (appendix p 12). Aggregated saliency maps indicated that the highlighted area along the arcade vessels was more prominent in images of higher scores (appendix p 13).

The clinical characteristics of the CMERC-HI participants by the tertile groups of RetiCAC score are detailed in the appendix (p 20). Median CAC scores were highest in the highest tertile group. The participants in the lowest tertile group had fewer cardiovascular disease events (n=5, 2·8%) than those in the highest tertile group (n=20, 11·4%; p=0·002). Similar findings were observed in the SEED study and the UK Biobank, where the participants in the low risk of RetiCAC group had fewer cardiovascular disease events (appendix pp 21–22).

Kaplan-Meier curves in CMERC-HI are given in figure 1. During the 5-year follow-up (median 4·1 years, IQR 3·8–4·5), 2164·4 person-years were examined. Kaplan-Meier curves show distinct cardiovascular disease risk stratification based on the tertiles of the RetiCAC scores. Similar to the current CT-measured CAC stratification system, the HRs of cardiovascular disease events showed a dose-response association across the three risk strata (risk-adjusted HR trend 2·02, 95% CI 1·18–3·46; table 3). Overall, in CMERC-HI, the proposed new stratification system based on RetiCAC score (C statistic 0·71, 95% CI 0·59–0·82) showed comparable performance in predicting cardiovascular disease events compared with conventional CT-measured CAC score (C statistic 0·71, 0·61–0·80; p=0·963; table 3).

In SEED and the UK Biobank, based on RetiCAC score, the risk-adjusted HRs for incident SCORE cardiovascular disease events showed a dose-response association across the three strata of RetiCAC, with HR trends of 1·33 (95% CI 1·04–1·71), and 1·21 (1·05–1·40), respectively (table 3). Improvement in predictive performance with the addition of RetiCAC to the cardiovascular disease risk models is provided in the appendix (p 23). Furthermore, because of the potential correlations between RetiCAC and other cardiovascular disease risk factors, we did a sensitivity analysis by using the proportion of RetiCAC uncorrelated from age, sex, and other clinical risk factors to predict cardiovascular disease events (appendix p 8), and the findings were similar.

The Kaplan-Meier analysis of cardiovascular disease events in the UK Biobank by the four groups of the PCE and three strata of RetiCAC are given in figure 2. In the borderline-risk group, the three strata of RetiCAC could further stratify the risk of SCORE cardiovascular disease events (HR trend 1·62, 95% CI 1·04–2·54, across the three RetiCAC strata). Similarly, in the

	Cardiovascular disease events/n	Person-years	Incidence*	Age-adjusted and sex-adjusted model		Risk-adjusted model†	
				HR (95% CI)	p value	HR (95% CI)	p value
CMERC-HI dataset							
CAC score							
0	6/217	895·2	0·7	1 (ref)	NA	1 (ref)	NA
>0–100	9/145	604·5	1·5	2·35 (0·80–6·89)	0·159	2·19 (0·74–6·50)	0·159
>100	18/165	664·7	2·7	4·18 (1·53–11·38)	0·005	3·34 (1·20–9·36)	0·021
HR trend	NA	NA	NA	1·51 (1·14–2·02)	0·005‡	1·40 (1·04–1·88)	0·024‡
C statistic	NA	NA	NA	0·67 (0·57–0·76)	NA	0·71 (0·61–0·80)	NA
RetiCAC score							
Low	5/176	721·7	0·7	1 (ref)	NA	1 (ref)	NA
Moderate	8/176	727·2	1·1	1·90 (0·58–6·77)	0·274	1·71 (0·49–5·98)	0·399
High	20/175	715·6	2·8	5·43 (1·63–18·07)	0·006	4·10 (1·22–13·77)	0·023
HR trend	NA	NA	NA	2·37 (1·37–4·09)	0·002‡	2·02 (1·18–3·46)	0·009‡
C statistic	NA	NA	NA	0·68 (0·58–0·79)	NA	0·71 (0·59–0·82)	NA
SEED dataset							
RetiCAC score for SCORE cardiovascular events							
Low	29/2327	24 547·2	0·1	1 (ref)	NA	1 (ref)	NA
Moderate	52/2966	30 944·4	0·2	1·26 (0·79–2·01)	0·338	1·04 (0·65–1·67)	0·856
High	229/3258	31 594·7	0·7	2·28 (1·38–3·77)	0·001	1·63 (0·98–2·69)	0·058
HR trend	NA	NA	NA	1·57 (1·22–2·01)	<0·001‡	1·33 (1·04–1·71)	0·023‡
C statistic	NA	NA	NA	0·77 (0·75–0·80)	NA	0·81 (0·79–0·83)	NA
RetiCAC score for ACC/AHA ASCVD events							
Low	152/2327	23 862·6	0·6	1 (ref)	NA	1 (ref)	NA
Moderate	240/2966	29 988·3	0·8	1·34 (1·09–1·66)	0·007	1·15 (0·93–1·42)	0·201
High	600/3258	29 675·9	2·0	2·07 (1·61–2·65)	<0·001	1·53 (1·19–1·96)	<0·001
HR trend	NA	NA	NA	1·45 (1·28–1·64)	<0·001‡	1·25 (1·10–1·41)	<0·001‡
C statistic	NA	NA	NA	0·71 (0·70–0·73)	NA	0·76 (0·74–0·77)	NA
UK Biobank dataset							
RetiCAC score for SCORE cardiovascular disease events							
Low	76/22 431	216 303·7	0·4	1 (ref)	NA	1 (ref)	NA
Moderate	140/14 624	136 340·1	1·0	1·60 (1·20–2·13)	0·001	1·51 (1·14–2·02)	0·005
High	121/10 624	95 520·9	1·3	1·64 (1·21–2·22)	0·001	1·54 (1·14–2·08)	0·005
HR trend	NA	NA	NA	1·25 (1·08–1·44)	0·002‡	1·21 (1·05–1·40)	0·008‡
C statistic	NA	NA	NA	0·77 (0·75–0·79)	NA	0·80 (0·77–0·82)	NA
RetiCAC score for ACC/AHA ASCVD events							
Low	360/22 431	213 039·3	1·7	1 (ref)	NA	1 (ref)	NA
Moderate	419/14 624	133 693·0	3·1	1·18 (1·02–1·37)	0·025	1·13 (0·98–1·31)	0·097
High	405/10 624	93 326·6	4·3	1·41 (1·21–1·64)	<0·0001	1·35 (1·16–1·57)	0·0001
HR trend	NA	NA	NA	1·19 (1·10–1·28)	<0·0001‡	1·16 (1·08–1·25)	0·0001‡
C statistic	NA	NA	NA	0·71 (0·70–0·73)	NA	0·74 (0·73–0·76)	NA

The C statistic values in the same row were from different models: age-adjusted and sex-adjusted model and all risk factors-adjusted model. n=number at risk. HR=hazard ratio. CMERC-HI=Cardiovascular and Metabolic Disease Etiology Research Center-High Risk Cohort. CAC=coronary artery calcium. NA=not applicable. RetiCAC=deep-learning retinal coronary artery calcium. SEED=Singapore Epidemiology of Eye Diseases. SCORE=Systematic COronary Risk Evaluation. ACC/AHA=American College of Cardiology/American Heart Association. ASCVD=atherosclerotic cardiovascular disease. *Incidence per 100 person-years for CMERC-HI and SEED, per 1000 person-years for the UK Biobank. †Risk-adjusted controlling for age, sex, hypertension, dyslipidaemia, diabetes, and smoking. ‡p value for trend.

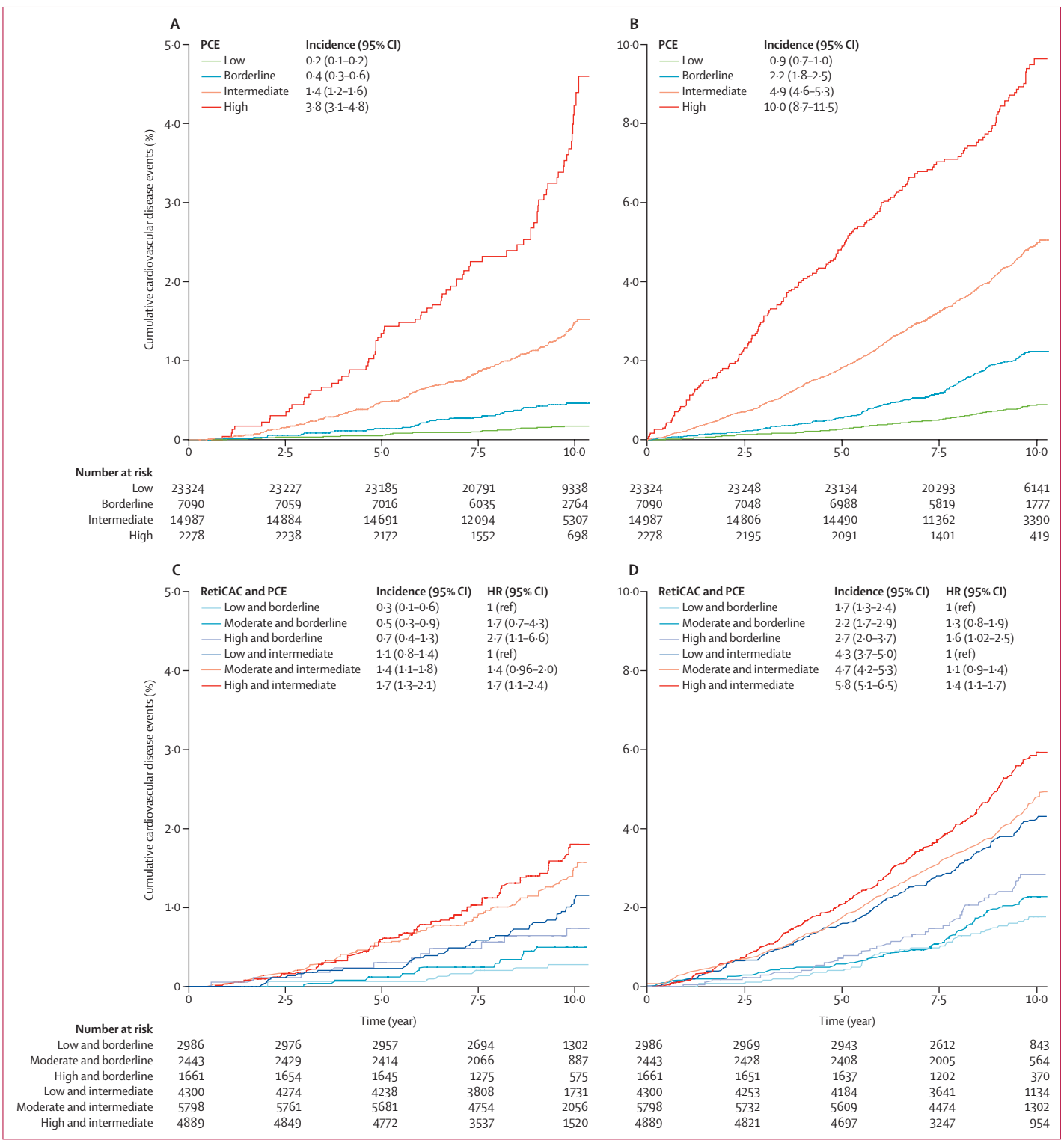
Table 3: **Risk of cardiovascular events by the deep-learning RetiCAC score and cardiac CT-measured CAC score**

intermediate-risk group, the three strata of RetiCAC also showed stratification of SCORE cardiovascular disease events (1·28, 1·07–1·54).

We also tested the incremental value of the RetiCAC score to PCE in predicting incident cardiovascular disease events, among the borderline-risk and intermediate-risk groups (table 4). By adding RetiCAC score to PCE, C statistics increased by 0·031 (95% CI 0·010–0·051) and the continuous NRI was 0·261 (95% CI 0·124–0·364) for prediction of SCORE cardiovascular disease events. Similarly, C statistics increased by 0·014 (95% CI 0·003–0·025) and the continuous NRI was 0·222 (95% CI

0·148–0·289) for prediction of ACC/AHA ASCVD events (table 4).

In the additional landmark analysis, we observed similar findings in risk stratification (appendix p 14). Sensitivity analyses that included individuals on statin therapy and all ethnic groups also showed results similar to those of the main analysis (appendix pp 15–16).



Discussion

In this study, we developed a deep-learning algorithm (RetiCAC) using retinal photographs to predict the presence of CAC. The RetiCAC scores showed superior performance compared with a single clinical parameter, such as age, glucose, or smoking status, in predicting the presence of CAC. We then proposed a novel three-tier cardiovascular disease risk stratification system based on RetiCAC score, which was comparable to the current three-tier CT-scan measured CAC scores in predicting cardiovascular disease events in a South Korean clinical cohort. The RetiCAC score was also able to stratify cardiovascular disease risk in an Asian general population comprising multiple ethnicities (Chinese, Malay, and Indian) in Singapore. Moreover, in a large British cohort of the UK Biobank, we showed RetiCAC could further stratify the cardiovascular disease risk in individuals classified by PCE as borderline-risk and intermediate-risk groups.

The novelty of the present study is further extending the previous work by Poplin and colleagues[12] to cardiac CT-measured CAC and its value in predicting future cardiovascular disease events and mortality. Recently, a deep-learning algorithm to predict abnormal CAC from retinal photographs was reported,[26] but the algorithm was not validated in independent datasets, and its ability to predict future cardiovascular disease events was not evaluated.

First, in the present study, we found that retina alone provided more information and signals for CAC prediction than any single clinical parameter, such as age or total cholesterol. The association among chronological age, CAC, and systemic atherosclerotic burden has been well established;[27] age and CAC might be viewed as a surrogate marker of atherosclerotic plaque burden, and age is one of the strongest predicting factors for CAC.[28] Nonetheless, our study confirms that the RetiCAC score is better than age and any other clinical parameters, for predicting the presence of CAC.

Second, our study confirmed the known links between retinal vascular damage (eg, retinal arteriolar narrowing, or retinopathy) and cardiovascular disease risk.[5] In saliency maps, retinal signs such as haemorrhage or cotton wool spots, which are known to be associated with cardiovascular disease risk,[5] were highlighted, implying that the algorithm accurately detected the clinically relevant retinal features to predict the presence of CAC.

Third, our study proposed that RetiCAC, a novel cardiovascular disease risk stratification system using relatively simple and non-radiation retinal photographs, was comparable to conventional CT-scan-measured CAC scores in predicting cardiovascular disease events. Moreover, using a large cohort, we showed that the added value of the RetiCAC score in improving cardiovascular disease risk stratification in borderline-risk and intermediate-risk groups in PCE in the UK Biobank. For example, after being further stratified based on RetiCAC score, the low-risk subgroup at intermediate risk from PCE and high-risk subgroup at borderline risk from PCE showed overlapped cumulative cardiovascular disease risk until 6-year follow-up (figure 2). This finding appears to be particularly useful in selecting patients for statin therapy if patients are undecided after clinician–patient risk discussion with consideration of risk enhancing factors. Although direct comparisons of NRI should be made with caution because definitions of the outcome and length of follow-up differ, the improvements by adding RetiCAC score to PCE in predicting cardiovascular disease events in the PCE borderline-risk and intermediate-risk groups (NRI of 22–26%) was somewhat lower to the previously reported improvement (NRI of 66%) by adding CAC to Framingham risk score in Yeboah and colleagues' study using Multi-Ethnic Study of Atherosclerosis (MESA) cohort.[29] However, this same group also reported NRI of 12% when CAC was added to the calibrated PCE using the same dataset.[30] Therefore, although the degree of improvement by RetiCAC in risk stratification was modest in this study, RetiCAC might still have a role for ASCVD risk assessment.

	SCORE cardiovascular disease events (n=223)	p value	ACC/AHA ASCVD events (n=804)	p value
RetiCAC	0·576 (0·542–0·611)	NA	0·543 (0·524–0·562)	NA
PCE	0·595 (0·572–0·618)	NA	0·579 (0·566–0·592)	NA
RetiCAC plus PCE	0·626 (0·595–0·657)	NA	0·593 (0·576–0·610)	NA
Δ RetiCAC plus PCE *vs* PCE*	0·031 (0·010–0·051)	0·0036	0·014 (0·003–0·025)	0·0133
NRI				
Continuous NRI (95% CI)	0·261 (0·124–0·364)	<0·0001	0·222 (0·148–0·289)	<0·0001
NRI positive, NRI negative	0·158, 0·103	NA	0·031, 0·192	NA

Data are C statistic (95% CI), unless stated otherwise. N=22 077. The RetiCAC plus PCE model is a logistic model fit on the UK Biobank. NRI for RetiCAC plus PCE versus PCE models and NRI in events group (NRI positive) and non-events group (NRI negative) were provided. SCORE=Systematic COronary Risk Evaluation. ACC/AHA=American College of Cardiology/American Heart Association. ASCVD=atherosclerotic cardiovascular disease. RetiCAC=deep-learning retinal coronary artery calcium score. NA=not applicable. PCE=Pooled Cohort Equation. NRI=net reclassification index. *Difference in C statistics between the model including RetiCAC plus PCE versus PCE alone.

Table 4: **Predictive performance with the addition of RetiCAC score to the PCE in the UK Biobank**

Figure 2: **Kaplan-Meier estimates for cumulative incidence of cardiovascular events in the UK Biobank**

Cumulative event rates of SCORE cardiovascular disease (primary outcome; A and C) and ACC/AHA ASCVD (secondary outcome; B and D) events stratified by the PCE (low-risk, borderline-risk, intermediate-risk, and high-risk groups; A and B) and the RetiCAC score (low-risk, moderate-risk, and high-risk groups) in PCE borderline-risk and intermediate-risk groups (C and D) in the UK Biobank (n=47 679). Incidence per 1000 person-years with HRs are provided. The three strata of RetiCAC could further stratify the risk of SCORE cardiovascular events with HR trend of 1·62 (95% CI 1·04–2·54) in PCE borderline-risk group and with HR trend of 1·28 (1·07–1·54) in PCE intermediate-risk group (C). The three strata of RetiCAC could further stratify the risk of AHA/ACC ASCVD events with HR trend of 1·26 (1·01–1·58) in PCE borderline-risk group and 1·18 (1·07–1·30) in PCE intermediate-risk group (D). PCE=Pooled Cohort Equation. RetiCAC=deep-learning retinal coronary artery calcium. SCORE=Systematic COronary Risk Evaluation. HR=hazard ratio. ACC/AHA=American College of Cardiology/American Heart Association. ASCVD=atherosclerotic cardiovascular disease.

A strength of this study was the use of large-scale CT data, which enabled us to use CAC—one of the most well established biomarkers of cardiovascular disease—for the deep-learning model development from retina photographs. Additionally, the added value of our new deep-learning-based biomarker was shown over the up-to-date clinical guideline (ie, PCE), using a representative European cohort with more than 10 years of follow-up.

However, our study had some limitations. First, RetiCAC, as a prognostic biomarker for cardiovascular disease, was validated in only South Korean participants, Singaporean (Chinese, Malay, and Indian) participants, and participants in the UK Biobank. In addition, sensitivity analysis including all ethnicities in the UK Biobank showed the RetiCAC as a biomarker for risk discrimination but meaningful analysis by detailed ethnicities was not possible due to small sample sizes. Therefore, further studies in other ethnicities and countries are needed. Second, there is a potential selection bias in our data because the training set was obtained from health screening centres and thus might not represent the general population. Third, the survival models that incorporate death and hospital inpatient data for the definition of incident cardiovascular disease might have introduced some misclassification in the SEED and UK Biobank due to the nature of administrative data. Fourth, in CMERC-HI, the cardiovascular disease outcomes were relatively rare for meaningful analysis due to a short follow-up period of 5 years. Therefore, we also included other-cause deaths as event outcomes. Fifth, further studies that include more CAC data are needed to test the performance changes for CAC prediction and directly compare cardiovascular disease risk prediction between CT-measured CAC score and RetiCAC. In addition, because of the scarcity of cohort data with well defined cardiovascular disease events and retinal photographs, we applied the US-based risk calculator for the UK population while SCORE is typically the risk calculator for the UK population. Therefore, further studies based on the US population such as the MESA study might provide more convincing evidence. Lastly, studies with enough outcomes data are needed to train the deep-learning algorithm to predict cardiovascular disease events directly from retinal photographs. There could be additional insights and improvements through training on ASCVD outcomes,

We developed a deep-learning algorithm to predict presence of CAC from retinal photographs. RetiCAC predicted the presence of CAC better than other risk factors alone. Based on this finding, we proposed a new simple cardiovascular disease risk stratification system (RetiCAC score in tertiles) with comparable performance with the conventional CAC measured by cardiac CT scan. Furthermore, using the RetiCAC score together with PCE enhances the ability to further stratify cardiovascular disease risk in general populations. Thus, retinal photography could potentially be adopted as a relatively simple and non-radiation imaging modality for cardiovascular disease risk classification.

Contributors

All authors reviewed the literature, contributed to data interpretation, and read and approved the final Article. THR, C-YC, and TYW conceptualised the study. THR, CJL, Y-CT, SSK, SP, C-YC, and TYW designed the study. CJL, YK, GL, YSC, YAK, SJB, SKK, BKL, HCK, SSK, SP, C-YC, and TYW collected the data. YK and GL developed the algorithm and THR, CCYC, and MY analysed data. THR, CJL, Y-CT, NC, YK, MY, DSWT, YSC, HCK, SSK, SP, C-YC, and TYW drafted the Article. NC, DSWT, HCK, S-MK, EYMW, SSK, SP, C-YC, and TYW critically revised the Article. THR, CJL, YK, GL, YSC, TKY, IHR, SJB, YAK, SKK, S-HL, BKL, S-MK, HCK, SSK, and SP confirm they had access to the datasets from South Korea. THR, Y-CT, NC, MY, DSWT, EYMW, CCYC, TYW, and C-YC confirm they had access to the datasets of the SEED and the UK Biobank study. THR, Y-CT, MY, TKY, CCYC, IHR, and C-YC accessed and verified each dataset during the course of the study.

Declaration of interests

THR was a former scientific adviser and owns stock of Medi Whale. GL and YK are employees of Medi Whale, and GL owns stock in Medi Whale. DSWT and TYW hold a patent on a deep-learning system for the detection of retinal diseases and this patent is not directly related to this study. DSWT is a cofounder of EyRiS. TYW has received consulting fees from Allergan, Bayer, Boehringer Ingelheim, Genentech, Merck, Novartis, Oxurion, Roche, and Samsung Bioepis. TYW is a cofounder of Plano and EyRiS. THR and GL hold the following patents that might be affected by this study: 10–2018–0166720(KR), 10–2018–0166721(KR), 10–2018–0166722(KR), and PCT/KR2018/016388, cardiovascular disease diagnosis assistant method and apparatus; and 62/715,729(US), method for predicting cardiocerebrovascular disease using eye image. These patents include content that can guide a prescription based on the risk stratification report by applying artificial intelligence to retinal photographs. All other authors declare no competing interests.

Data sharing

The UK Biobank test dataset was obtained from UK Biobank (application number 45925). Data cannot be shared publicly due to the violation of patient privacy and the absence of informed consent for data sharing. Data from South Korea are available to researchers who meet the criteria for access to confidential data; requests should be made to Sung Soo Kim, Department of Ophthalmology, Severance Hospital, Yonsei University, Seoul, South Korea (semekim@yuhs.ac) and Sungha Park, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University, Seoul, South Korea (shpark0530@yuhs.ac). Requests for data from the SEED should be made to Ching-Yu Cheng, Singapore Eye Research Institute, Singapore (chingyu.cheng@duke-nus.edu.sg).

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