



# BMJ Open Association between deep learning measured retinal vessel calibre and incident myocardial infarction in a retrospective cohort from the UK Biobank

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## ABSTRACT

**Background** Cardiovascular disease is a leading cause of global death. Prospective population-based studies have found that changes in retinal microvasculature are associated with the development of coronary artery disease. Recently, artificial intelligence deep learning (DL) algorithms have been developed for the fully automated assessment of retinal vessel calibres.

**Methods** In this study, we validate the association between retinal vessel calibres measured by a DL system (Singapore I Vessel Assessment) and incident myocardial infarction (MI) and assess its incremental performance in discriminating patients with and without MI when added to risk prediction models, using a large UK Biobank cohort.

**Results** Retinal arteriolar narrowing was significantly associated with incident MI in both the age, gender and fellow calibre-adjusted (HR=1.67 (95% CI: 1.19 to 2.36)) and multivariable models (HR=1.64 (95% CI: 1.16 to 2.32)) adjusted for age, gender and other cardiovascular risk factors such as blood pressure, diabetes mellitus (DM) and cholesterol status. The area under the receiver operating characteristic curve increased from 0.738 to 0.745 (p=0.018) in the age–gender-adjusted model and from 0.782 to 0.787 (p=0.010) in the multivariable model. The continuous net reclassification improvements (NRIs) were significant in the age and gender-adjusted (NRI=21.56 (95% CI: 3.33 to 33.42)) and the multivariable models (NRI=18.35 (95% CI: 6.27 to 32.61)). In the subgroup analysis, similar associations between retinal arteriolar narrowing and incident MI were observed, particularly for men (HR=1.62 (95% CI: 1.07 to 2.46)), non-smokers (HR=1.65 (95% CI: 1.13 to 2.42)), patients without DM (HR=1.73 (95% CI: 1.19 to 2.51)) and hypertensive patients (HR=1.95 (95% CI: 1.30 to 2.93)) in the multivariable models.

**Conclusion** Our results support DL-based retinal vessel measurements as markers of incident MI in a predominantly Caucasian population.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Large dataset of over 30 000 participants with a long follow-up period of up to 11 years.
- ⇒ Limited cross-ethnic generalisability due to an exclusively Caucasian-based study population.
- ⇒ Limited evaluation of the effect of cardiovascular disease treatments such as antihypertensives on retinal vessel calibre is observed due to the relatively low incidence rate of myocardial infarction.
- ⇒ Possible result interference from retinal pathologies on fundus photographs should be considered.

## INTRODUCTION

As of 2019, ischaemic heart disease accounts for 49.2% of cardiovascular mortality worldwide.<sup>1</sup> Over the years, various risk models have been developed for predicting the incidence and mortality from cardiovascular diseases (CVD), such as the Framingham Risk Score, Pooled Cohort Equation and QRISK. However, these risk scores often underestimate or overestimate CVD risk when evaluated on different ethnic populations.<sup>2–3</sup> Moreover, these equations were based on indirect biochemical cardiovascular parameters (eg, total cholesterol, glycated haemoglobin (HbA1c)) but not through direct assessment of vessel integrity.

The retinal microvasculature, visualised through retinal fundus images, can serve as a direct, non-invasive ‘window’ that reflects the integrity of systemic vascular health, such as that of the coronary microcirculation.<sup>4</sup> The simplicity of obtaining retinal images compared with blood biochemistry makes it an attractive option for supplementing cardiovascular risk prediction, on top of existing risk scores.<sup>5–6</sup> Previous studies have



revealed associations between various retinal parameters and cardiovascular health, such as retinal vessel tortuosity,<sup>7</sup> arteriovenous nicking and signs of retinopathy such as microaneurysms, haemorrhages, exudates, etc.<sup>8,9</sup> Retinal vessel calibre is one of the parameters most well established and accepted by the research community.<sup>10,11</sup> Nevertheless, human grading and evaluation of retinal fundus images are time-consuming, spanning an average of 25 min and subject to both intragrader and intergrader variability,<sup>12</sup> making it difficult to conduct large-scale screening.

Deep learning (DL), as a branch of artificial intelligence (AI), has recently been applied to assess retinal vasculature automatically by using convolutional neural networks (CNNs).<sup>13,14</sup> In the field of using retinal imaging for CVD risk evaluation, these networks typically predict one of four primary outcomes, namely retinal features (e.g., retinal calibre), CVD risk factors (e.g., smoking status), CVD biomarkers (e.g., Coronary Artery Calcium Score) and direct CVD event prediction.<sup>15</sup> However, the 'black-box' phenomenon inherent to DL algorithms – referring to the lack of interpretability of a DL algorithm's logic behind its decision-making – has stirred up ethical and legal controversies of AI's utility in making life-or-death clinical decisions. To enhance interpretability, DL systems may be tailored to focus on regions of interest in a retinal image that are known to be associated with CVD. For example, it is reported that retinal vessel calibre estimated by a recently developed DL system, namely the Singapore I Vessel Assessment (SIVA-DLS) software, was correlated with CVD risk factors such as blood pressure and HbA1c, incident CVD events and CVD mortality.<sup>13</sup> However, such analysis was based on predominantly Asian datasets, and generalisability to other ethnicities is yet to be shown. This study aimed to further validate the association of retinal vessel calibres measured by SIVA-DLS with myocardial infarction (MI) and to assess the incremental performance of incorporating retinal vessel calibre measurements into existing cardiovascular risk factors for MI risk evaluation in a predominantly Caucasian population, using retrospective data from the UK Biobank.

## METHODS

### Study population

The retinal fundus images used in this study were taken from the UK Biobank. The UK Biobank dataset was generated in a large-scale study of more than 500 000 participants aged ranging from 40 to 69 years between 2006 and 2010, who underwent a series of health examinations to provide a resource for the scientific community to identify genetic and environmental risk factors for diseases within the middle-to-older age group in the UK population. A subset of 85 728 participants also underwent ophthalmic imaging such as retinal fundus photography, in which 35 918 participants possess the necessary SIVA-DLS parameters required for this study.<sup>16</sup> Baseline assessment was carried out between 7 December 2009

and 7 June 2013. The participants were followed up until 18 March 2020.

### Retinal imaging and image evaluation

The SIVA-DLS is a CNN using retinal fundus images to measure retinal vessel calibre. The detailed development, training, testing and validation process of the model have been mentioned in a previous study.<sup>13</sup> The UK Biobank database comprises of single-field fundus photographs centred to include both the macula and the optic disc.<sup>16</sup> In this study, the SIVA-DLS was trained for 300 epochs, focusing on fully automated measurements of retinal vessel calibres within the area between 0.5 and 2.0 disc diameters away from the optic disc margin. The SIVA-DLS automatically assigns weightings to features on retinal photographs to compute the values of central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) for the width of retinal arteriole and retinal venules, respectively.

### Primary outcome

The primary outcome of this study was incident MI, which was defined by an algorithm developed by the UK Biobank based on the International Classification of Diseases 10th Revision (ICD-10) codes I21-I25. This algorithm combined information from self-reported medical conditions, operations and medications, hospital admissions and death registries after the code date of baseline assessment.<sup>17</sup>

### Statistical analysis

All statistical analyses were performed using R language (R V.3.5.3, R Foundation for statistical computing 2019, Vienna, Austria). One eye of each participant was randomly selected for the statistical analyses. Retinal vessels calibres were analysed in quartiles as well as continuous variables (per each SD increase). In the quartile analysis, fourth quartile was used as the reference for CRAE, while first quartile was used as the reference for CRVE.<sup>13</sup>

Multivariable Cox-proportional hazards models were performed to examine the association between retinal vessel calibre and incident MI, adjusting for age, gender, cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, smoking status, diabetes mellitus (DM), use of antihypertensive drugs, body mass index, history of atrial fibrillation (AF) and flutter, use of cholesterol-lowering drugs, socioeconomic status and fellow calibre (ie, CRAE is included as an independent variable in the CRVE model and vice versa) as covariates. We adjusted for these parameters based on previous studies illustrating their associations with incident MI.<sup>18</sup> Use of antihypertensive drugs and cholesterol-lowering drugs was defined by records in self-reported medications. DM was defined by self-reported or clinically diagnosed DM. Socioeconomic status was categorised by Townsend deprivation index using national cut-off points (high: < -2.08; middle ≥ -2.08 to < 1.40; low ≥ 1.40).<sup>18</sup> History of AF and flutter was defined by ICD-10 code I48 from multiple data

sources including primary care, hospital admission and self-reported medical condition data.

To evaluate the performances of the models, we calculated the area under the receiver operating characteristic curves (AUCs) for discriminating between those with and without incident MI. The AUC of the model with retinal vessel calibres was compared with that of the model without retinal vessel calibres using the bootstrap method with 2000 bootstrap replicates. We also computed the continuous net reclassification improvements (NRI) after adding CRAE and CRVE into the models. We performed subgroup analysis to test for potential effect modification of risk factors (age, gender, smoking status, DM and hypertension) in the relationship between retinal vascular calibre and incident MI. P value of  $<0.05$  was considered statistically significant.

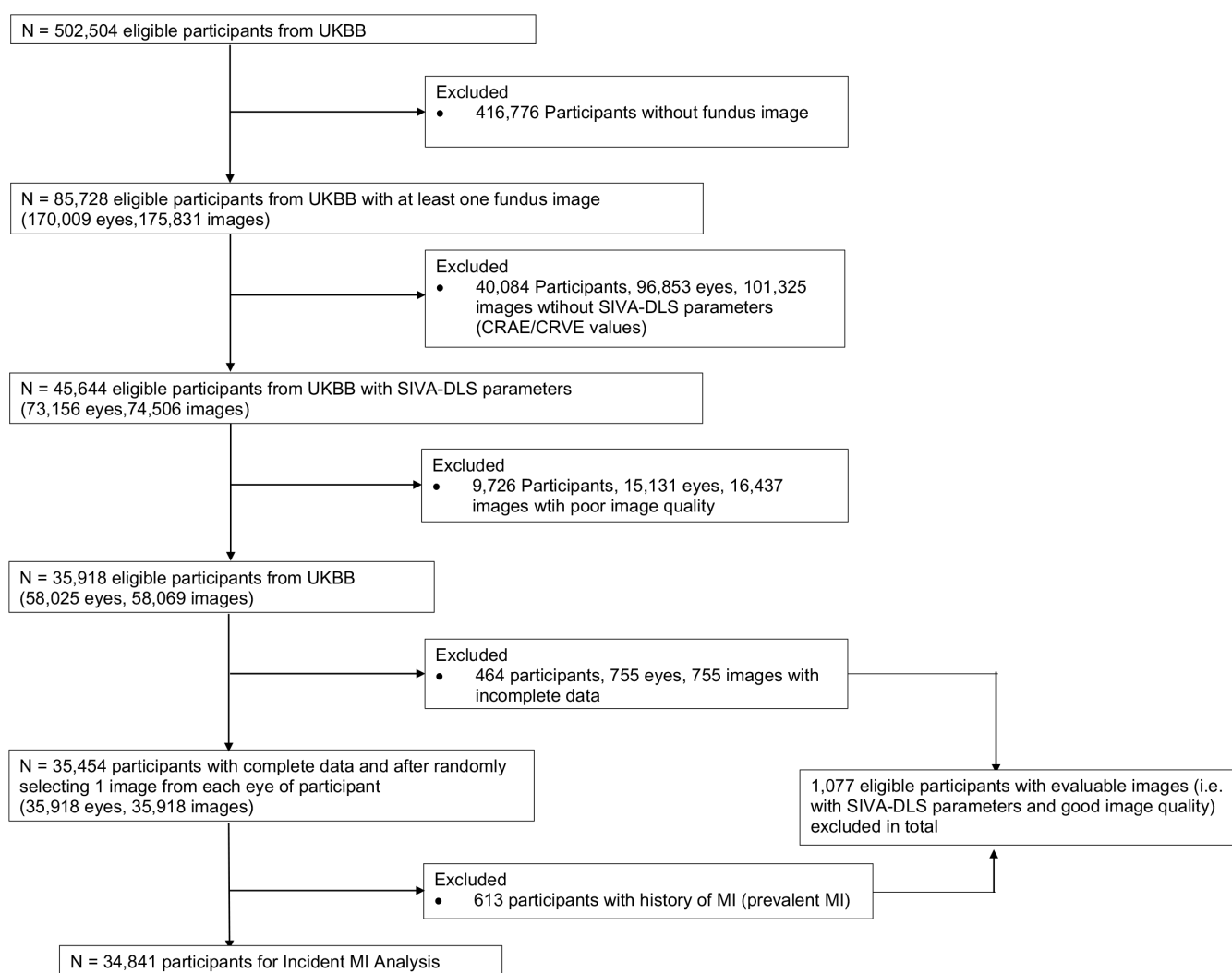
### Patient and public involvement

Patients and the general public were not involved in the entire research process.

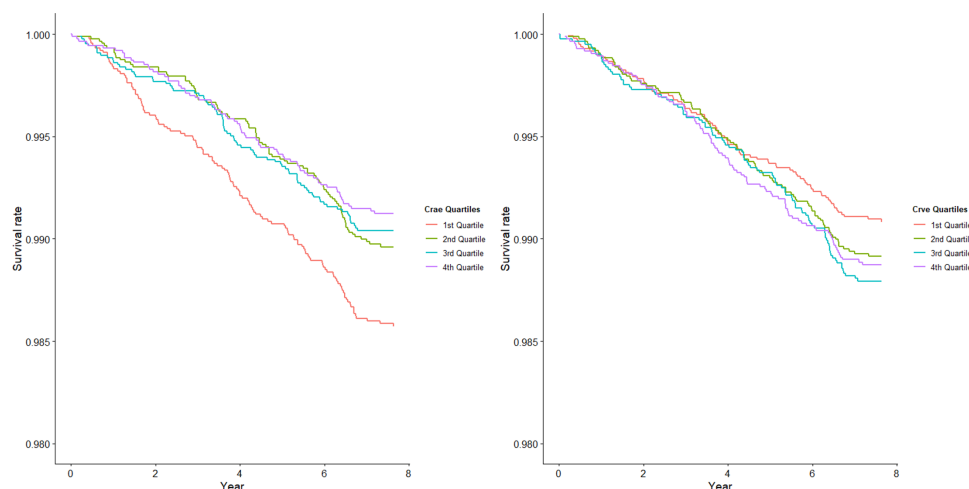
### RESULTS

Figure 1 describes the participant selection process. Study participants without retinal images or CRAE/CRVE parameters, and those with poor image quality or incomplete data were excluded from this study. Since there were no labels on the gradability of the fundus photographs in the UK Biobank data, we employed a recently developed DL algorithm to filter out ungradable photographs that were not suitable for our analysis.<sup>19</sup> Among those with evaluable retinal images, a total of 1077 participants were excluded due to incomplete data (including information on covariates) and a previous history of MI. Figure 2 describes the expected survival rates from patients with different CRAE/CRVE quartiles. Participants with CRAE in the first quartile demonstrated significantly reduced survival rates compared with participants with higher CRAE.

Table 1 describes the demographic data of the UK Biobank dataset. After excluding the participants who did not fit in the criteria, 34841 participants were included for the analysis of incident MI. Over the



**Figure 1** Flowchart of study selection process. CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; MI, myocardial infarction; SIVA-DLS, Singapore I Vessel Assessment; UKBB, UK Biobank.



**Figure 2** Survival curves showing the expected survival rates from patients in different quartiles of retinal arteriolar calibre and retinal venular over the follow-up period under the multivariable model.

follow-up period, 375 participants developed incident MI.

**Table 2** describes the HRs and AUCs for incident MI. In the model adjusted for age, gender and fellow calibre only, a narrower CRAE at baseline was associated with incident MI when evaluated both by quartiles (HR 1.67 (95% CI: 1.19 to 2.36),  $p=0.003$ , comparing first to fourth quartile as reference), and per SD increase (HR 0.86 (95% CI: 0.75 to 0.98),  $p=0.028$ ). Wider CRVE is only associated with incident MI when evaluated by quartiles (HR 1.51 (95% CI: 1.06 to 2.13),  $p=0.021$ , comparing fourth to first quartile as reference). The AUC increased significantly

from 0.738 to 0.745 ( $p=0.018$ ) when CRAE and CRVE are included in the models adjusted for age and gender. In the multivariable model, a narrower CRAE at baseline was associated with incident MI when evaluated by quartiles (HR 1.64 (95% CI: 1.16 to 2.32),  $p=0.005$ , comparing first to fourth quartile as reference). Although no significant associations were observed between CRVE and incident MI, the AUC increased significantly when CRAE and CRVE were included in the multivariable models, both when evaluated by quartiles (from 0.782 to 0.787,  $p=0.010$ ) or by per SD increase (from 0.782 to 0.785,  $p=0.030$ ). The continuous NRIs were significant in both

**Table 1** Demographics of the UK Biobank population in the current data analysis

	Participants excluded, n=1077		Participants Included, n=34841		P value
			Without Incident MI, n=34466	With Incident MI, n=375	
Age, year	60.27 (7.44)*	56.46 (8.23)*	60.89 (6.77)*		<0.001
Male, n (%)	688 (63.9)*	15 190 (44.1)*	268 (71.5)*		<0.001
Ethnicity, white, n (%)	1077 (100)*	34 466 (100)*	375 (100)*		/
Total cholesterol level, mmol/L	4.98 (1.27)*	5.75 (1.12)*	5.67 (1.34)*		0.170
HDL level, mmol/L	1.32 (0.36)*	1.51 (0.39)*	1.30 (0.34)*		<0.001
Systolic BP, mm Hg	139.09 (18.20)*	138.91 (19.38)*	145.78 (18.42)*		<0.001
Diastolic BP (SD), mm Hg	79.30 (10.71)*	81.78 (10.61)*	84.05 (10.64)*		<0.001
Current smoker, n (%)	95 (8.8)*	2789 (8.1)*	58 (15.5)*		0.042
Diabetes mellitus, n (%)	118 (11.0)*	1313 (3.8)*	43 (11.5)*		0.012
Use of antihypertensive drugs, n (%)	548 (50.9)*	5920 (17.2)*	129 (34.4)*		<0.001
BMI, kg/m <sup>2</sup>	28.47 (5.10)*	26.97 (4.58)*	28.26 (4.65)*		<0.001
HbA1c, %	5.7 (2.9)*	5.4 (2.7)*	5.7 (3.0)*		0.033
History of AF, n (%)	135 (12.5)*	1218 (3.5)*	62 (16.5)*		<0.001
Use of cholesterol-lowering drugs, n (%)	623 (57.8)*	5339 (15.5)*	128 (34.1)*		<0.001
Socioeconomic status					
High, n (%)	519 (49.8)*	16 906 (49.1)*	189 (50.4)*		0.719
Middle, n (%)	325 (31.2)*	11 284 (32.7)*	108 (28.8)*		0.390
Low, n (%)	198 (19.0)*	6276 (18.2)*	78 (20.8)*		0.556

P-values of less than 0.05 were considered statistically significant.  
 \*Data are presented as mean (standard deviation) or numbers (percentage).  
 AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein;

**Table 2** Cox proportional-hazards regression models for the association between of retinal arteriolar calibre and retinal venular calibre with incident myocardial infarction

	Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value
<b>CRAE</b>				
First quartile	1.67 (1.19 to 2.36)	<b>0.003</b>	1.64 (1.16 to 2.32)	<b>0.005</b>
Second quartile	1.20 (0.86 to 1.67)	0.290	1.18 (0.85 to 1.65)	0.321
Third quartile	1.10 (0.79 to 1.51)	0.576	1.10 (0.79 to 1.51)	0.576
Fourth quartile	Reference			
<b>CRVE</b>				
First quartile	Reference			
Second quartile	1.25 (0.93 to 1.69)	0.144	1.19 (0.88 to 1.61)	0.264
Third quartile	1.44 (1.05 to 1.97)	<b>0.023</b>	1.32 (0.96 to 1.81)	0.083
Fourth quartile	1.51 (1.06 to 2.13)	<b>0.021</b>	1.23 (0.87 to 1.76)	0.244
AUC after adding CRAE and CRVE‡	0.745*	<b>0.018</b>	0.787†	<b>0.010</b>
CRAE per SD increase	0.86 (0.75 to 0.98)	<b>0.028</b>	0.89 (0.78 to 1.02)	0.095
CRVE per SD increase	1.09 (0.95 to 1.24)	0.208	0.99 (0.86 to 1.13)	0.833
AUC after adding CRAE and CRVE§	0.742*	0.069	0.785†	<b>0.030</b>
	<b>Continuous NRI, % (95% CI)</b>	<b>P value</b>	<b>Continuous NRI, % (95% CI)</b>	<b>P value</b>
Continuous NRI after adding CRAE and CRVE	21.56 (3.33 to 33.42)	<b>0.013</b>	18.35 (6.27 to 32.61)	<b>0.013</b>

Model 1 was adjusted for age, gender and fellow calibre (ie, CRAE is included as an independent variable in the CRVE model and vice versa) only. Model 2 (multivariable model) was adjusted for age, gender, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, smoking status, diabetes mellitus status, use of antihypertensive drugs, body mass index, history of atrial fibrillation and flutter, use of cholesterol-lowering drugs, socioeconomic status and fellow calibre.

\*AUC by age and gender only before adding CRAE and CRVE=0.738.

†Multivariable AUC before adding CRAE and CRVE=0.782.

‡AUC calculated with CRAE/CRVE treated by quartile, using 10-year incidence as cut-off. P values evaluated the comparisons of AUC under models with and without CRAE and CRVE.

§AUC calculated with CRAE/CRVE treated as continuous variables, using 10-year incidence as cut-off. P values evaluated the comparisons of AUC under models with and without CRAE and CRVE.

AUC, area under the receiver operating characteristic curve; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; NRI, net reclassification improvement.

the age-adjusted and gender-adjusted model (NRI=21.56 (95% CI: 3.33 to 33.42),  $p=0.013$ ) and the multivariable model (NRI=18.35 (95% CI: 6.27 to 32.61),  $p=0.013$ ), indicating significant classification improvements after the addition of retinal parameters.

We also stratified the participants by age, gender, smoking status, DM and hypertensive status for incident MI analysis, and the results are presented in online supplemental tables 1–5. The results for online supplemental tables 1a, 2a, 3a, 4a and 5a include the subgroup analyses based on age, gender and/or fellow calibre-adjusted models, and online supplemental tables 1b, 2b, 3b, 4b and 5b include the subgroup analyses based on multivariable models.

In the multivariable analysis stratified by age (online supplemental table 1b), narrower CRAE was associated with incident MI among participants aged above 50 (HR 1.58 (95% CI: 1.09 to 2.28),  $p=0.015$ , comparing first and fourth quartile as reference). The AUC increase was significant among those under 50 years of age in the model evaluated by quartiles, from 0.834 to 0.887 ( $p=0.003$ ). In the multivariable analysis stratified by gender (online supplemental

table 1b), a narrower CRAE is significantly associated with incident MI among males (HR 1.62 (95% CI: 1.07 to 2.46),  $p=0.024$ ) but not for females. In the multivariable analysis stratified by smoking status (online supplemental table 3b), a narrower CRAE was associated with incident MI (HR 1.65 (95% CI: 1.13 to 2.42,  $p=0.010$ ), comparing first quartile and fourth quartile as reference) for non-smokers. CRVE was significantly associated with incident MI (HR 3.77 (95% CI: 1.22 to 11.66),  $p=0.021$ , comparing fourth and first quartile as reference) for smokers. In the multivariable analysis stratified by DM (online supplemental table 4b), narrower CRAE was associated with incident MI among non-diabetics (HR 1.73 (95% CI: 1.19 to 2.51),  $p=0.004$ , comparing first and fourth quartile as reference). CRVE was significantly associated with incident MI (HR 3.22 (95% CI: 1.08 to 9.56),  $p=0.035$ , comparing third and first quartile as reference) for diabetics. In the multivariable analysis stratified by hypertensive status (online supplemental table 5b), narrower CRAE was associated with incident MI among hypertensive patients (HR 1.95 (95% CI: 1.30 to 2.93),  $p=0.001$ , comparing first and fourth quartile as reference).



## DISCUSSION

In this study, we further validated the association between retinal vessel calibres measured by a previously developed DL model (SIVA-DLS) and MI in a Caucasian cohort. The strength of the model lies in the fact that it focuses on automated retinal vessel calibre measurement instead of evaluating the entire retinal image, enabling better interpretability of the results generated by the DL model. In this study, we showed that retinal arteriolar narrowing was associated with incident MI with improvements in discriminative performance when retinal vessel calibres were added to the prediction models. When the study population was stratified by age, gender, smoking status, DM status and hypertensive status, overall, such associations remained generally consistent.

Previous disease-specific evaluations on DL systems to predict CVD have only been done on entities such as atherosclerosis<sup>20</sup> and stroke.<sup>8</sup> Our study adds to the existing literature by demonstrating an association between retinal arteriolar narrowing, as measured by a DL-based algorithm, and MI.

In our analysis, retinal arteriolar narrowing is associated with an increased risk of incident MI. The pattern is generally consistent when adjusted for different cardiovascular risk factors, with the only exception seen in the multivariable models when evaluated by per SD increase. This may imply that retinal arteriolar narrowing is associated with MI only at a particular range of arteriolar calibre, such as the narrowest arterioles. This is supported by the quartile analysis, where significant associations were only seen for the first quartile. Such an association is reasonable, since both MI and retinal arteriolar narrowing involve gradual ischaemic changes and vascular impairments in the heart and retina, causing damage in the respective organs.<sup>21 22</sup> Adding retinal vessel calibres into existing risk factors also improved discriminative performance, suggesting the possible application of non-invasive parameters such as age and gender in preliminary MI screening. This will be particularly useful in less developed countries, where the facilities required to assess biochemical parameters for cardiovascular risk stratification may not be easily available.<sup>23</sup> While our study demonstrated statistical significance in improving discrimination and the potential of SIVA-DLS in predicting MI risk, the relatively modest numerical improvements in our study encourage additional large-scale, cross-ethnic investigations to further validate its true clinical significance.

We also conducted stratified analysis based on the participants' age, gender, smoking status, DM status and hypertensive status to evaluate the applicability of the algorithm in well-established high-risk groups. In the age-stratified model, there is a significant improvement in discrimination when CRAE/CRVE was added into the risk prediction models, particularly in those aged under 50 where the significance persisted in both the gender-adjusted and multivariable models. This is consistent with previous studies illustrating the larger degree of retinal arteriolar narrowing among the young population,

possibly due to the greater arteriolar sclerosis among the old.<sup>24</sup> This supports the utilisation of retinal vessel calibre changes for evaluation of cardiovascular risk in the young population, in which clinical manifestations of CVD are usually more indolent. For the gender analysis, while CRAE is more significantly associated with incident MI among men like the overall analysis, we also found significant association between CRVE and incident MI among women. Existing evidence also supports a stronger association of retinal vessel calibre and cardiovascular events among women than men, possibly due to their more diffuse atherosclerosis, stiffer aortas and higher incidence of dysfunctional microcirculation than men.<sup>25</sup> In addition, we also found that the association between narrower CRAE and incident MI is stronger among hypertensive participants, indicating that such calibre changes may reflect more profound hypertension, a known risk factor for MI.

Another point to note is that while the associations between CRVE and incident MI are relatively non-specific among different quartiles of venular calibre, the respective association for CRAE is consistently evident among the narrowest quartile of arteriolar calibre. The reason behind the non-specificity among CRVE quartiles is not well understood; it is not well known whether the extent of CRVE widening directly reflects the severity of inflammation in the coronary circulation. In addition, incident MI as a multifactorial process also involves complex interactions among platelets, coagulation factors and other molecules,<sup>26</sup> which may not have been adequately reflected from the CRVE values. Lastly, we also found significant associations between CRVE and incident MI among smokers and diabetics, but these results should be taken with caution due to the wide CIs associated with these hazard ratios. Some studies have suggested that retinal venular widening among smokers may be associated with reduced oxyhaemoglobin causing hypoxia and downstream dilation of retinal venules,<sup>27</sup> while that among diabetics may be associated with elevated inflammatory and endothelial dysfunction markers.<sup>28 29</sup> Such mechanisms are also seen in coronary artery disease,<sup>30</sup> although the exact correlation between retinal venular widening and MI remains to be elucidated.

The significance of the study lies in the fact that it further validates the ability of retinal imaging to confer additional benefits in screening for patients at risk of CVDs. This could be particularly useful for patients already having to attend regular ophthalmic examinations, such as those with diabetic retinopathy who commonly have increased CVD risk.<sup>31</sup> Annual eye examinations are recommended for diabetic patients and are currently conducted in primary care settings in certain parts of the world, such as the general outpatient clinics in Hong Kong.<sup>32</sup> The incorporation of CVD risk assessment into routine retinal photography would enable closer monitoring of the patients' cardiovascular health and promote early treatment. Although annual diabetic eye examinations are yet to be widely available in primary care settings worldwide,

the rapid development of other imaging modalities such as smartphone-based fundus imaging may play a role in expanding the scope of coverage of retinal photography, and thus hopefully enable the incorporation of CVD risk assessment into the monitoring regime in the future. Automated measurements and analyses of CVD risk from retinal vessel calibres measured by DL models may also act as an initial population screening tool to speed up CVD screening due to their large handling capacities to identify at-risk patients for definitive tests and treatment follow-up. This could be particularly useful in less-developed areas without comprehensive laboratory facilities.<sup>23</sup> A higher screening capacity would also improve understanding on the CVD risk profile within the population, which also promotes healthcare decision-making by reallocating resources to the population most vulnerable to CVD such as MI.

The strengths of this study include a large dataset of over 30 000 participants and a long follow-up period of 7–11 years. Our study also focused on one particular disease entity—MI, instead of previous evaluations focusing on a more non-specific disease spectrum of CVDs such as MI together with stroke.<sup>13</sup>

There were a few limitations to this study. First, this study focused only on the white ethnicity and thus is limited in cross-ethnic generalisability. Although such generalisability can be partially demonstrated when coupled with previous studies featuring a diverse Asian population,<sup>13</sup> the primary outcomes of the previous study also include stroke, so the two studies may not be directly comparable. Also, due to our relatively small number of participants who eventually developed MI, we could not evaluate the influence of different cardiovascular treatments such as antihypertensives and cholesterol-lowering drugs on CRAE measurements of this population longitudinally, and thus their effects on our MI risk prediction model. In addition, despite having excluded ungradable images unsuitable for our analysis using a recently developed DL algorithm,<sup>19</sup> there may remain certain images with retinal pathologies which may interfere with the study results. Moreover, in contrast to previous studies using SIVA which used optic disc-centred fundus photographs, the UK Biobank uses single-field fundus photographs covering both the macula and optic disc, which was unable to cover totally the region 0.5 to 2.0 disc diameters away from the disc margin. Nevertheless, the heatmaps generated by SIVA-DLS are still able to highlight the major retinal vessels for estimating CRAE and CRVE. Lastly, our results may not be accurate enough to reflect the relevant associations among the younger population. Previous studies on SIVA-DLS using other cohorts demonstrated a larger proportional bias between human-generated vessel calibre values (SIVA-human) and those generated by SIVA-DLS for larger CRAE values, which is common in the younger population.<sup>13</sup> Unfortunately, we do not have SIVA-human parameters available in our UK Biobank cohort, thus we are unable to evaluate any improvements on such bias in our study. Further studies

will be important to evaluate SIVA-DLS's translatability to the younger age group.

## CONCLUSION

We have further validated that narrowed retinal arteriolar calibre measured by the previously developed DL model is associated with incident MI, supporting the importance of the retinal microvasculature in reflecting early microvascular damage of coronary vessels associated with MI development. This encourages further evaluation of the clinical significance of the DL model in enhancing the efficiency and accuracy of MI risk evaluation in the future, including its potential clinical application for non-invasive CVD risk screening.

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**Contributors** Concept and design: CYC, CCheng and TYW. Technical support (coding of the deep learning system): DX, MLL and WH. Data analysis: CChong and MY. Critical evaluation and interpretation of the results: DY, MY and YLW. Initial draft of the manuscript: YLW. Critical revision of the manuscript for important intellectual content: CYC, CCheng, CChong, DX, DY, MLL, MY, TYW, WH and YLW. Final approval of the manuscript: CYC. Supervision, overall responsibility and guarantor: CYC.

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**Competing interests** CYC, DX, MLL and TYW are the coinventors of the SIVA-DLS system. TYW is an inventor, hold patents and is a cofounder of start-up companies EyRis and Visre, which have interests in and develops digital solutions for eye diseases including diabetic retinopathy. In addition, personal consulting fees were made from the following companies: Aldropika Therapeutics, Bayer, Boehringer Ingelheim, Carl Zeiss, Genentech, Iveric Bio, Novartis, Oxurion, Plano, Roche, Sanofi and Shanghai Henlius.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by the UK Biobank from the North West Multi-centre Research Ethics Committee (MREC), National Health Service, UK, Reference ID: 21/NW/0157. The study was performed in accordance with the principles of the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available.

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