JACC: ADVANCES VOL. 3, NO. 12, 2024

ORIGINAL RESEARCH

Blood Pressure Predicted From Artificial Intelligence Analysis of Retinal Images Correlates With Future Cardiovascular Events

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ABSTRACT

BACKGROUND High systolic blood pressure (SBP) is one of the leading modifiable risk factors for premature cardiovascular death. The retinal vasculature exhibits well-documented adaptations to high SBP and these vascular changes are known to correlate with atherosclerotic cardiovascular disease (ASCVD) events.

OBJECTIVES The purpose of this study was to determine whether using artificial intelligence (AI) to predict an individual's SBP from retinal images would more accurately correlate with future ASCVD events compared to measured SBP.

METHODS 95,665 macula-centered retinal images drawn from the 51,778 individuals in the UK Biobank who had not experienced an ASCVD event prior to retinal imaging were used. A deep-learning model was trained to predict an individual's SBP. The correlation of subsequent ASCVD events with the AI-predicted SBP and the mean of the measured SBP acquired at the time of retinal imaging was determined and compared.

RESULTS The overall ASCVD event rate observed was 3.4%. The correlation between SBP and future ASCVD events was significantly higher if the AI-predicted SBP was used compared to the measured SBP: 0.067 v 0.049, $P = 0.008$. Variability in measured SBP in UK Biobank was present (mean absolute difference = 8.2 mm Hg), which impacted the 10-year ASCVD risk score in 6% of the participants.

CONCLUSIONS With the variability and challenges of real-world SBP measurement, AI analysis of retinal images may provide a more reliable and accurate biomarker for predicting future ASCVD events than traditionally measured SBP. (JACC Adv. 2024;3:101410) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 20, 2024; revised manuscript received September 26, 2024, accepted October 8, 2024.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101410

ABBREVIATIONS AND ACRONYMS

AI = artificial Intelligence

ASCVD = atherosclerotic cardiovascular disease

CVD = cardiovascular disease

DL = Deep Learning

ICD = International Classification of Diseases

MAE = mean absolute error

PCE = pooled cohort equation

SBP = systolic blood pressure

UKBB = UK Biobank

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide.[1] High systolic blood pressure (SBP) is the leading modifiable risk factor for premature cardiovascular deaths, and it has been estimated that high SBP accounted for 10.8 million cardiovascular deaths in 2021.[2] Prospective cohort studies report a continuous log-linear association between SBP and mortality across diverse population groups with and without pre-existing CVD. They also demonstrate that reducing the SBP significantly reduces the risk of death due to vascular events.[3,4] SBP is therefore an important predictor of future atherosclerotic CVD (ASCVD) risk and is central to personalizing preventive therapy.[5]

The retina offers a unique window into an individual's vascular health, being the only location where the vasculature can be directly visualized. There is a large body of evidence that indicates that changes in the retinal vasculature can be used to predict the risk of CVD events. The Blue Mountains eye study was the first to demonstrate that changes in retinal vascular caliber, specifically arteriolar narrowing and venule widening, predicted CVD death independent of traditional CVD risk factors in men and women aged 49 to 75 years.[6] It is now accepted that mild hypertensive retinopathy, especially generalized arteriolar narrowing and enhanced arteriolar wall reflex, is positively associated with stroke risk even in hypertensive patients with good blood pressure control.[7] It has also been demonstrated that mild hypertensive retinopathy is positively associated with CVD risk even in normotensive individuals[8] and that individuals with better cardiovascular health had a lower prevalence of retinopathy and were less likely to have narrow arterioles and wide venules, compared to those with poorer cardiovascular health.[9] Until now, these biomarkers were largely inaccessible, requiring specialist reading centers, but advances in artificial intelligence (AI), and deep learning (DL) in particular, have created new opportunities for analyzing retinal images. Not only is it now possible to extract data about traditional retinal diseases such as diabetic retinopathy,[10,11] these algorithms can also analyze subtle patterns in the retinal images to predict a range of nonocular health conditions. In addition to providing novel ways of analyzing an individual's risk of experiencing CVD, this emerging field of oculomics also provides new ways of assessing the relationship between traditional biomarkers, like SBP and CVD.[12,13]

We hypothesize that the observed vascular changes that develop in the retina are related to an individual's cumulative exposure to high SBP. Thus, a DL algorithm trained on retinal images to predict SBP may show better correlation with future ASCVD events than standard cuff measurements of SBP. We therefore studied individuals in the UK Biobank (UKBB) who had retinal images and relevant biometric data to compare the association of SBP and subsequent ASCVD events when: 1) the SBP was predicted by a DL model trained on retinal images; 2) the SBP was acquired by cuff measurement.

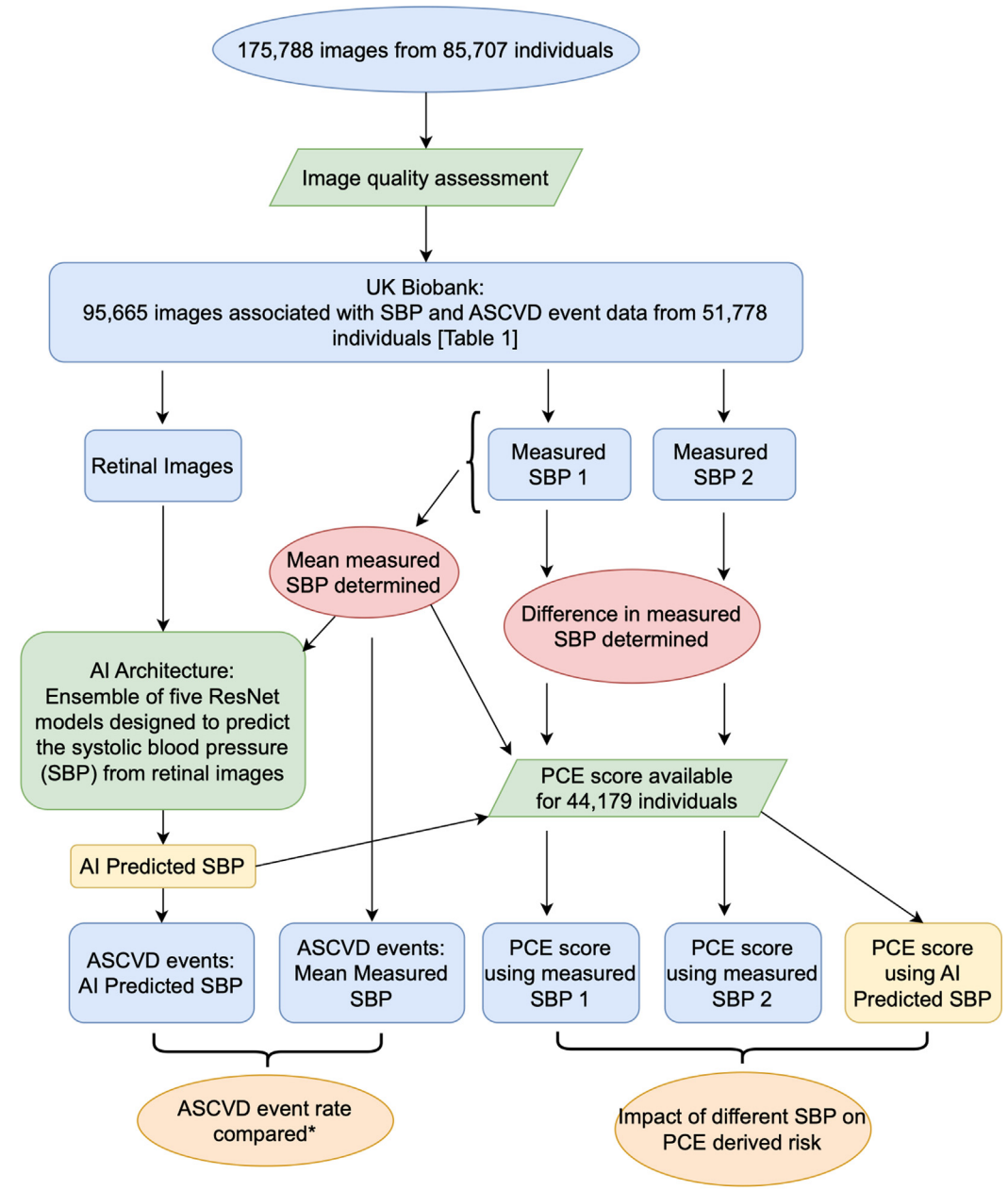
METHODS

ETHICS STATEMENT. Our research adhered to the protocols and approvals governed by the UKBB. This approval, initially granted in 2011 and subsequently renewed in 2021, signifies the compliance of the UKBB with prevailing research standards. Furthermore, we obtained a material transfer agreement with the UKBB dated the 28th of March 2022, under application number 86299, to ensure the responsible use and secure transfer of de-identified data.

DATA SOURCE. 95,665 macula-centered retinal images drawn from the 51,778 individuals in the UKBB who had not experienced an ASCVD event prior to the acquisition of the retinal image were used in this study. The definition of ASCVD events used was derived from the ICD10/9 codes held in the UKBB. This list is presented in the Supplemental Appendix. The overall design of our study is summarized in **Figure 1**. As the UKBB comprises images of varying quality, the images were first passed through a DL image quality screening system to identify those that were of sufficient quality to train and test a DL model to predict SBP from the retinal image.[14] Images of insufficient quality, non-macular-centered and duplicate images were removed. Next, the UKBB dataset was interrogated to ensure that those subjects with images that of adequate quality had their SBP recorded. The demographic and relevant biometric data from these 51,778 individuals is shown in **Table 1**.

These images were then randomly split into 70%:15%:15% for training, validation, and testing, respectively. In summary, 85% of the images were utilized to train and validate the DL model to predict SBP. To ensure that the model's predictions were based solely on the visual cues present in the images and remained unbiased to any supplementary clinical data including ASCVD events, during training, the model was restricted to accessing only the retinal images and the mean SBP reading measured at the

FIGURE 1 Flow Chart Illustrating Experiment Methodology



AI = artificial intelligence; ASCVD = atherosclerotic cardiovascular disease; PCE = pooled cohort equation; SBP = systolic blood pressure.

time the image was acquired. The remaining 15% of images were reserved as a hold-out dataset to assess the performance of the SBP prediction model compared against actual recorded SBP readings.

We then compared the relationship between the AI-predicted SBP with future ACSVD events versus the cuff measured SBP. As the incidence of future ASCVD events in the UKBB was low, we utilized the

TABLE 1 Demographics of Those Individuals in the UK Biobank Dataset Used in This Study

	Overall (N = 51,778)	Training and Validation set (n = 43,754)	Hold-out Test set* (n = 8024)
Age (y)	56.8 ± 8.3	56.9 ± 8.3	56.6 ± 8.3
Systolic blood pressure (mm Hg)	136.9 ± 18.4	137.0 ± 18.4	137.0 ± 18.2
Diastolic blood pressure (mm Hg)	81.48 ± 10.0	81.4 ± 10.1	81.4 ± 10.0
AI-predicted SBP (mm Hg)	138.1 ± 5.8	138.1 ± 5.8	137.9 ± 5.8
HbA1c (mmol/mol)	35.9 ± 6.3	35.9 ± 6.3	36.0 ± 6.6
Total cholesterol (mg/dL)	220.4 ± 44.0	220.4 ± 43.8	220.0 ± 44.7
HDL cholesterol (mg/dL)	57.6 ± 15.1	57.7 ± 15.1	57.5 ± 15.0
Sex assigned at birth			
Male	2349 (45%)	19,784 (45%)	3625 (45%)
Female	28,369 (55%)	23,970 (55%)	4399 (55%)
Smoker			
Current	6723 (13.0%)	5609 (12.8%)	1090 (13.6%)
Previous	13,301 (25.7%)	11,073 (25.3%)	2182 (27.2%)
Never	31,754 (61.4%)	27,072 (61.9%)	4752 (59.2%)
Diabetes	2483 (4.80%)	2084 (4.76%)	384 (4.79%)
Race/ethnicity			
Non-Hispanic White	93.1%	93.1%	93.1%
South Asian	2.1%	2.1%	2.2%
East Asian	0.3%	0.4%	0.3%
Black/African American	2.1%	2.2%	2.0%
Multiracial	0.8%	0.7%	0.8%
Other	1.2%	1.1%	1.2%
Prefer not to answer	0.4%	0.4%	0.4%
ASCVD events	1,779 (3.4%)	1,479 (3.4%)	292 (3.6%)

Values are mean ± SD or n (%). *2-sample t-test for continuous variables (age, blood pressure, HbA1c, cholesterol, etc) and chi-square test for categorical variables (sex, smoker, diabetes, race, etc) were performed on the development set and hold-out test datasets. There was no significant difference between the demographics of either cohort.

entire dataset of 51,778 individuals for this component of the study.

DEVELOPMENT OF A DL MODEL TO PREDICT SBP.

Measured SBP from the UKBB. The UKBB dataset recorded 2 SBP readings for each participant visit at least 1 minute apart after 5 minutes of seated rest using an Omron 705 IT electronic BP monitor (OMRON Healthcare).[15] For the purposes of the current study, the measured SBP was the mean of the 2 recorded SBP readings recorded in the UKBB.

AI SBP prediction Model Development and assessment. The AI SBP prediction model comprised an integrated ensemble of 5 deep learning models, each an iteration of the ResNet architecture. The ensemble approach enhances the predictive reliability and accuracy of the model by amalgamating the outputs of each of the component models to establish a consensus on the final prediction of the SBP value. In brief, the convolutional neural networks utilized the InceptionResnet-V2 and ResNet50 models, with specific modifications to suit our objectives. For example, one convolutional neural network model utilizes a design consisting of 164 layers, integrating both inception and residual blocks. Inception blocks are employed to amalgamate convolutional layers with various filter sizes, facilitating the capture of a wide range of features. Concurrently, residual blocks support the propagation of learning across layers using skip connections, enhancing the model's ability to learn from complex patterns. Further refinements, including batch normalization and the introduction of bottleneck layers, were also integrated into the design to elevate the efficiency of the training process. To facilitate efficient training, the AI SBP prediction model was trained on an NVIDIA GPU with 48 GB of high-speed memory.

In preparation for processing, the retinal images were subjected to background noise reduction and resized to a uniform dimension of 800 × 800 pixels. Parameter optimization during the training phase was achieved using the Adam optimizer, set at a learning rate of 10e-3. This approach, coupled with a dropout rate of 0.2, was calibrated to minimize loss and mitigate the risk of overfitting, ensuring that the models remained generalizable to new, unseen data.

The only input to the model was the retina image. The measured SBP was used as the training target and consequently the trained model served as a

mathematical function, f(x) = y, where x is the retina image and y is the predicted SBP.

Assessing the relationship between AI-predicted SBP and measured SBP and subsequent ASCVD events. The strength of the associations between the future observed ACSVD events and both the AI-predicted and the measured SBP was investigated using Pearson's correlation statistic. After using regression analysis to adjust for potential confounders including age, sex, smoking status, and diabetes and to establish the independent predictive value of SBP derived from retinal images, the significance of the correlations to future ASCVD events of AI-predicted SBP vs measured SBP was compared using Fisher z-transformation. The rationale for selecting the 4 confounders listed was threefold: clinical relevance, to prevent overfitting of the AI prediction model, and model parsimony. A more detailed of the rationale for this decision is presented in the Supplemental Appendix. The approach detailed above transforms the correlation coefficients into a z-score that follows a normal distribution, making it possible to compare the 2 correlations directly. The formula to compute the z-score difference is:

$$z = \frac{\tanh^{-1}(r_1) - \tanh^{-1}(r_2)}{\sqrt{\frac{1}{N-3} + \frac{1}{N-3}}}$$

where r1 and r2 are the 2 correlation coefficients and N is sample size (51,778). To evaluate whether the observed difference between r1, r2 was statistically significant, we compared the calculated z-score against the standard normal distribution.

A comparison of ASCVD event rates across AI-predicted SBP and the measured SBP was evaluated using chi-squared tests. We then conducted a sub analysis to investigate the impact of: 1) an individual's sex assigned at birth; and 2) taking medication for hypertension, on the relationship between AI-predicted SBP, measured SBP, and future ASCVD events.

Assessing the relationship between AI-predicted SBP and measured SBP and 10-year ASCVD risk score. To assess the impact of the different SBP measures on the ASCVD risk score issued to an individual, we calculated the 10-year ASCVD risk issued by the pooled cohort equation (PCE) to every individual using the 2 SBP measurements in the UKBB and the AI-predicted SBP. The impact of using different SBP measurements on the 10-year ASCVD risk scores was then compared. To investigate the relationship between time to an event and the type of SBP used, the time elapsed between the retinal photograph and the ASCVD event was calculated. Individuals were then ranked by the measured SBP and the AI-predicted SBP. Both groups were then grouped into quartiles and the time to event in each quartile compared.

Statistical methods. Continuous variables, such as SBP, were represented as mean ± SD. Categorical variables, such as demographic information (eg, sex, race), were represented as counts and percentages. Where appropriate, we categorized the population into relevant subgroups based on clinical variables, such as the presence of diabetes, hypertensive, and ASCVD events. These subgroups were used for stratified analyses to assess how the model performed across different patient cohorts.

Pearson correlation coefficients were calculated to evaluate the strength of association between AI-predicted SBP and traditionally measured SBP. This allowed us to quantify how well the AI model's predictions aligned with real-world SBP measurements.

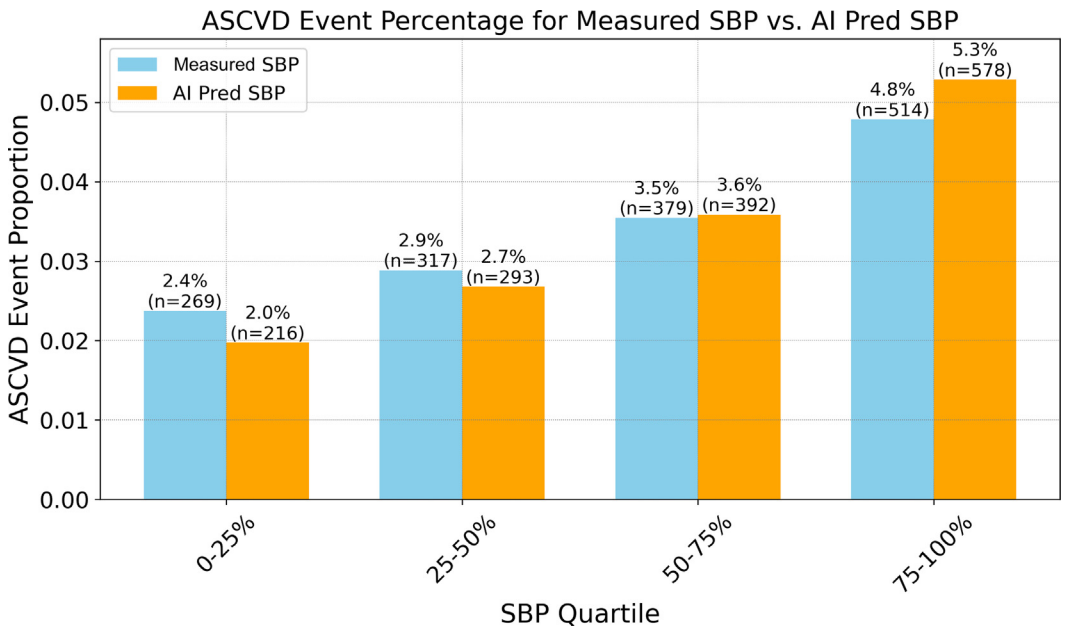
The performance of the AI SBP prediction model was evaluated by comparing the AI-predicted SBP with the measured SBP across the test set by evaluating the mean absolute error (MAE) between the AI-predicted SBP for every individual and the measured SBP.

To compare the model's predictive power for future ASCVD events, Cox proportional hazards regression models were used to calculate hazard ratios for both AI-predicted SBP and measured SBP, along with 95% confidence intervals. The hazard ratios were adjusted for covariates such as age, sex, smoking status, and diabetes, allowing us to isolate the impact of SBP on ASCVD outcomes.

Area under the receiver-operating characteristic curve was calculated to assess the model's performance in predicting ASCVD events based on both AI-predicted SBP and measured SBP. To quantify improvements in prediction, we calculated the Net Reclassification Index (NRI) to determine whether using AI-predicted SBP resulted in better classification of individuals into high or low risk of ASCVD events compared to measured SBP.

To assess whether differences between AI-predicted SBP and measured SBP were statistically significant, we used paired *t*-tests for continuous variables and chi-square tests for categorical variables. For comparing the predictive performance of AI-predicted SBP with measured SBP, we used the z-test to evaluate whether the difference in correlation coefficients (or area under the receiver operating characteristic curve values) was statistically significant.

FIGURE 2 Future ASCVD Event Rates Categorized by SBP Assessment Method



Comparison of the future atherosclerotic cardiovascular event rates when individuals were ranked by AI-predicted SBP or measured SBP, sub divided by quartiles. Total cohort size 51,778. Correlation between ASCVD events and measured SBP: 0.049, Correlation between ASCVD events and AI-pred SBP: 0.067: Difference $P = 0.008$. AI = artificial intelligence; ASCVD = atherosclerotic cardiovascular disease; SBP = systolic blood pressure.

Before applying the 2-sample *t*-tests to compare continuous variables, we assessed the normality of the data using the D'Agostino-Pearson test, which is well-suited for large population datasets. This test evaluates both skewness and kurtosis, making it more reliable for detecting meaningful deviations from normality in large samples. The variables we tested for normality included SBP, diastolic blood pressure, HbA1c, total cholesterol, and HDL cholesterol.

For all parameters, the D'Agostino-Pearson test results indicated normal or near-normal distribution of the data. Additionally, the large sample size in our study makes the *t*-test robust to slight deviations from normality, further supporting its use.

RESULTS

PERFORMANCE OF THE DL MODEL TO PREDICT MEASURED SBP. The MAE of the AI-predicted SBP compared to measured SBP was 12.35 mm Hg, with an R^2 of 0.21. When the cohort was divided into those on medication for hypertension and those not, and those who were male or female, the MAEs were similar (12.50 mm Hg for those on hypertension medication and 12.33 mm Hg for those not; males: 11.36 mm Hg and 13.17 mm Hg for females). The Bland-Altman plot of the AI-predicted and measured SBP (Supplemental Figure 1) reveals that the means are very similar, but the AI model has a narrower prediction range than the measured SBP. This is not unexpected as the mathematical processes underlying AI model training force it to aim for a "mean" value to minimize its "error function."

RELATIONSHIP BETWEEN ASCVD EVENTS, AI-PREDICTED SBP, AND MEASURED SBP. The overall ASCVD event rate in this study was 3.4%. The correlation between AI-predicted SBP and future ASCVD events was significantly stronger than when the mean of the measured SBP was used (0.067 vs 0.049, $P = 0.008$) (z-score statistics −2.644). Whether individuals were ranked by AI-predicted SBP or measured SBP, when the quartiles were examined, the ASCVD event rate increased in both groups from Q1 to Q4 (**Figure 2**).

RELATIONSHIP BETWEEN ASCVD EVENTS, AI-PREDICTED SBP, AND MEASURED SBP CATEGORIZED BY SEX ASSIGNED AT BIRTH. The demographics of individuals subdivided according to whether they were male or female are shown in Supplemental Table 1. Males were older, had statistically significant higher SBP, and higher rates of diabetes and smoking, but had

lower cholesterol levels. The ASCVD event rate in males was almost 3 times higher than in females (5.2% vs 1.9%). In both sexes, the incidence of ASVCD events increased in both groups from Q1 to Q4 (**Figures 3A and 3B**). In males, the correlation between AI-predicted SBP and future ASCVD events was significantly stronger than when the mean of the measured SBP was used (0.065 vs 0.025; $P < 0.001$). This trend was not observed in females (0.056 vs 0.058; $P = 0.89$). Comparison of the mean SBP in individuals when ranked by the measured SBP and then the AI-predicted SBP revealed that for both sexes, the mean measured SBP was significantly lower than mean AI-predicted SBP. Conversely, the mean of the measured SBP was significantly higher in those individuals in Q4 when the cohort was ranked by measured SBP compared to AI-predicted SBP.

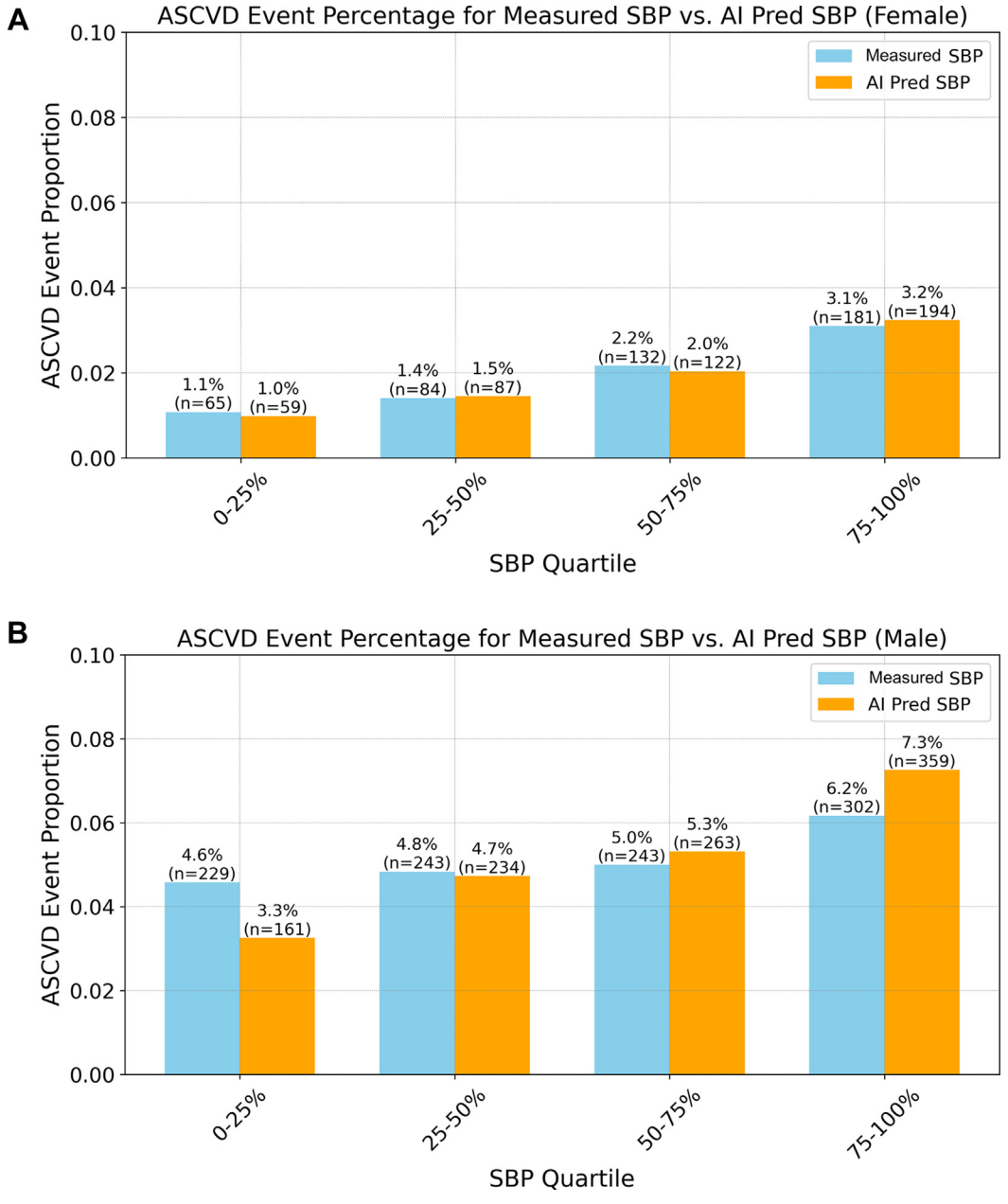
RELATIONSHIP BETWEEN ASCVD EVENTS, AI-PREDICTED SBP, AND MEASURED SBP CATEGORIZED BY HYPERTENSION MEDICATION STATUS. The demographics of individuals subdivided according to whether they were taking medication for hypertension is shown in Supplemental Table 2. Individuals on medication for hypertension in the subgroup of the UKBB used in our study were more likely to be male, were older, had statistically significant higher SBP, had higher rates of diabetes, and had lower cholesterol levels. They were also more likely to be on cholesterol-lowering medications. The ASCVD event rate in individuals taking medication for hypertension was 4 times higher than in those not taking medication for hypertension (8.5% vs 2.1%) (**Figures 4A and 4B**). In those taking medication for hypertension, there was a negative correlation between ASCVD events and both the measured and the AI-predicted SBP, but the strength of this correlation was significantly greater for the measured compared to the AI-predicted SBP: (−0.058 v −0.006; $P < 0.001$). The distribution of ASCVD events differed among those taking a BP medication. A greater proportion of ASCVD events was observed for measured SBP Q1 than AI-predicted SBP Q1 and a lower proportion of ASCVD events was observed for measured SBP Q4 than AI-predicted SBP Q4. In the subgroup of individuals not on medication for hypertension, the incidence of ASVCD events increased in both groups from Q1 to Q4 (**Figure 4B**), but there was no significant difference in the rate of ASCVD events whether individuals were ranked by AI-predicted SBP or measured SBP ($P = 0.70$).

RELATIONSHIP BETWEEN PCE-CALCULATED 10-YEAR ASCVD RISK SCORE AND AI-PREDICTED SBP VS MEASURED SBPs. There was sufficient data within the dataset to calculate the PCE score for 10-year ASCVD risk for 44,179 individuals (**Figure 1**). The PCE ASCVD risk scores generated depending upon which UKBB SBP measurement was taken are shown in **Table 2**. The population mean of the 2 SBP readings recorded in the UKBB that were used in this study was 136.6 ± 18.1 mm Hg. The spread of the absolute difference between the first and second SBP readings recorded is shown in **Figure 5**. The mean absolute difference was 8.2 mm Hg. Typically, the second reading was 5.6 mm Hg lower than the first. The proportion of individuals allocated intermediate or high risk (PCE score ≥7.5%) compared to those allocated low/borderline risk (PCE score <7.5%) was significantly higher if the first SBP measurement was taken ($P < 0.001$). When the AI-predicted SBP was used, individuals allocated lower risk by the PCE had the lowest proportion of ASCVD events. Use of the AI-predicted SBP also yielded the highest proportion of individuals with ASCVD events who were allocated higher risk. The relative risk of an ASCVD event was 13% higher if the AI-predicted SBP was used compared to if the mean of the measured SBP was used. This trend for the AI-predicted SBP to better predict ASCVD events did not achieve statistical significance (**Table 2**). The NRI for the AI-predicted SBP compared to the measured SBP was 2.6%. There was no significant difference in the time to event regardless of which method was used for SBP (Supplemental Table 3).

DISCUSSION

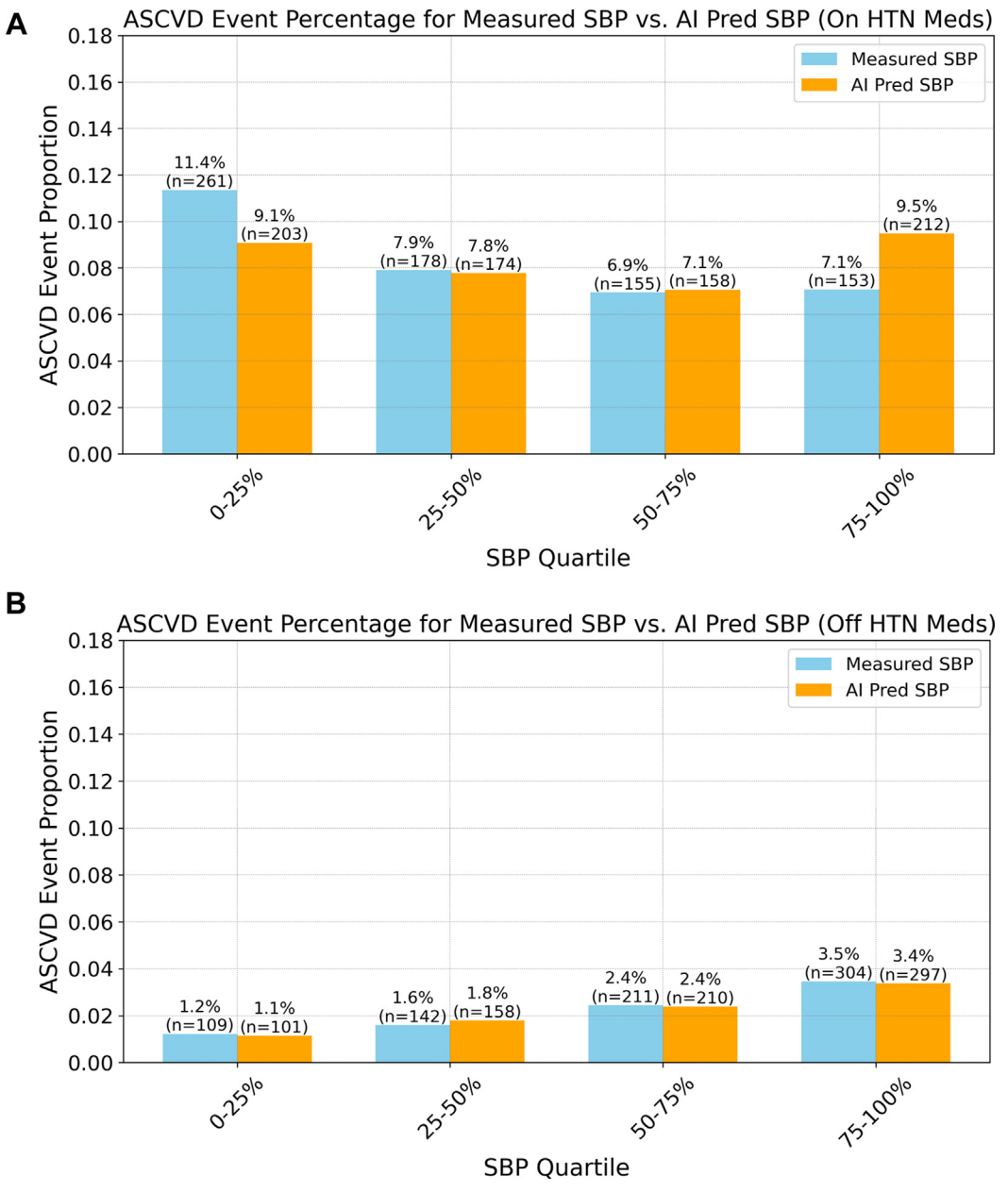
The main novel finding in this study was that SBP predicted from AI analysis of retinal images correlated more strongly with future ASCVD events compared to traditionally measured SBP in a large UK population (0.067 vs 0.049, $P = 0.008$) (**Central Illustration**). We also found that using the AI-predicted SBP for calculating the PCE improved the prediction of future ASCVD events compared to if the measured SBP was used (13% increase in relative risk, NRI 2.6%). The Atherosclerosis Risk in Communities study[16] demonstrated that both narrower retinal arterioles and wider retinal venules confer long-term risk of mortality due to ASCVD and the likelihood of experiencing an ASCVD event was related to the magnitude of these vascular changes. A similar relationship between the magnitude of the microvascular changes and ASCVD events was reported by McGeechan et al.[17] who found that every 20 μm increase in venular diameter was associated with a 15% higher risk for stroke. A recent review, summarizing the available evidence concluded that the evidence-base for using the retinal microvasculature to quantify

FIGURE 3 Future ASCVD Event Rates Subcategorized by Sex Assigned at Birth



Comparison of the future ASCVD event rate in (A) females and (B) males ranked by AI-predicted SBP or measured SBP by quartiles. (A) Females: Cohort size 28369. ASCVD event rate: 1.9%. Correlation between ASCVD events and measured SBP: 0.056, Correlation between ASCVD events and AI-predicted SBP: 0.058: Difference $P = 0.89$. Comparison of ASCVD events in both Q1 and Q4 for AI-predicted versus measured SBP. $P < 0.001$. (B) Males: Cohort size 23409. ASCVD event rate: 5.2%. Correlation between ASCVD events and measured SBP: 0.025, Correlation between ASCVD events and AI-predicted SBP: 0.065: Difference $P < 0.001$. Comparison of ASCVD events in both Q1 and Q4 for AI-predicted versus measured SBP. $P < 0.001$. AI = artificial intelligence; ASCVD = atherosclerotic cardiovascular disease; SBP = systolic blood pressure.

FIGURE 4 Future ASCVD Event Rates Subcategorized by Hypertensive Medication Usage



Comparison of the future ASCVD event rate (A) for individuals taking hypertension medications; (B) for individuals not taking hypertension medications, both ranked by AI-predicted SBP or measured SBP; sub divided by quartiles. 4a. Taking hypertension medications: Cohort size 10,501. ASCVD event rate: 8.5%. Correlation between ASCVD events and measured SBP: -0.058, correlation between ASCVD events and AI-predicted SBP: -0.006: Difference $P < 0.001$. Comparison of ASCVD events in both Q1 and Q4 for AI-predicted versus measured SBP $P < 0.005$. (B). Not taking hypertension medications: Cohort size 41,277. ASCVD event rate: 2.1%. Correlation between ASCVD events and measured SBP: 0.061, correlation between ASCVD events and AI-predicted SBP: 0.060: Difference $P = 0.80$. Comparison of ASCVD events in both Q1 and Q4 for AI-predicted versus measured SBP. $P < 0.001$. AI = artificial intelligence; ASCVD = atherosclerotic cardiovascular disease; SBP = systolic blood pressure.

TABLE 2 Pooled Cohort Equation-Calculated 10-Year ASCVD Risk Score Generated

	Low/Borderline 10-Year Risk PCE score <7.5%	Intermediate/High 10-Year Risk PCE score ≥7.5%
Using first measured SBP reading to calculate PCE	638/30,890 (2.07%)†	875/13,289 (6.58%)†
Using second measured SBP reading to calculate PCE	748/32,929 (2.27%)†	765/11,250% (6.80%)†
Using mean of the 2 measured SBP readings to calculate PCE	685/31,970 (2.14%)†	828/12,209 (6.78%)†
Using AI-predicted SBP reading to calculate PCE	675/32,803 (2.06%)†	838/11,376 (7.37%)†

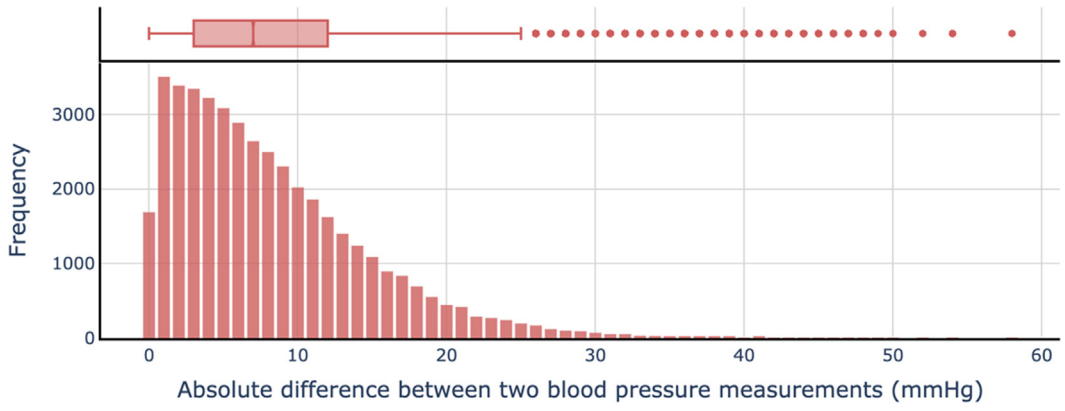
Values are n/N (actual event rate). $P < 0.001$ Difference in the proportion of individuals allocated high risk depending upon whether the first or second SBP was used, whether the first or the mean measured SBP was used, and whether the second or mean measured SBP was used. $P = 0.61$ difference in the proportion of individuals allocated high risk depending upon whether the second measured SBP or AI-predicted SBP was used. Compare ASCVD rate in lower PCE risk (<7.5%) group where PCE is calculated using AI-predicted SBP and mean measured SBP reading (2.06% vs 2.14%): Chi-square = 0.527, $P = 0.468$. Compare ASCVD rate in higher PCE risk (≥7.5) group where PCE is calculated using AI-predicted SBP and mean measured SBP reading (7.37% vs 6.78%): Chi-square = 2.976, $P = 0.084$. Details of the score issued depending upon which systolic blood pressure measure; (AI-predicted or the measured SBP) was used. A Pooled Cohort Equation score could only be calculated for 44,179 cases as there was insufficient patient data (diabetes status, smoking status, cholesterol data, medications history, race, sex assigned at birth, age) to calculate this PCE score for the remainder. †Actual observed event rate in this cohort (%).

ASCVD = atherosclerotic cardiovascular disease.

systemic CVD risk was "strong" and could be a clinically useful tool to support both primary and secondary disease prevention strategies.[18] Although further corroboration is required, our findings suggest that it is possible to train a DL model to read these retinal biomarkers and that the SBP so derived can be used to predict the likelihood of an individual experiencing an ASCVD event.

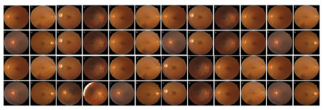
Sub analysis based on sex-assigned at birth, and whether the individual was on hypertension medication, yielded interesting findings. Males were older, had higher levels of most risk factors (SBP, diabetes, and smoking) but had lower cholesterol levels. They had higher ASCVD events and the AI-predicted SBP was better correlated with ASCVD events than the measured SBP. Females had much lower ASCVD event rates and the correlations with AI-predicted SBP vs measured SBP with ASCVD events was no longer significantly different. Those on hypertension medications were exclusively male and there was a strong correlation between being on hypertension medications and cholesterol-lowering medications. No female was on either hypertension or cholesterol-lowering medications in this UKBB cohort. The profound differences in the cohorts used for our sub analysis make it difficult to draw too many conclusions about the relative impact of the 2 SBP measures on ASCVD risk in them. For the subgroup of individuals on hypertension medications, the risk of an event was broadly flat across all quartiles when they were ranked the AI-predicted SBP. Conversely there was a negative correlation between measured SBP and ASCVD events when individuals were ranked by measured SBP. The finding that the cuff-measured

FIGURE 5 Distribution of the Absolute Difference Between SBP Measurements



Distribution of the absolute difference between the first and second SBP measurements of those individuals in the UK Biobank who were used in this study. SBP = systolic blood pressure.

CENTRAL ILLUSTRATION **Blood Pressure Predicted From Artificial Intelligence Analysis of Retinal Images Correlates With Future Cardiovascular Events**



95,665 Macula-Centered Retinal Images From the 51,778 Individuals in the UK Biobank

Deep-learning model trained to predict systolic blood pressure (SBP)

Main Findings

- ASCVD event rate was 3.4%
- Correlation between SBP and ASCVD events was significantly higher if the AI-predicted SBP was used compared to the measured SBP (P = 0.008)

Conclusion

AI analysis of retinal images may provide a more reliable and accurate marker for predicting future ASCVD events than traditionally measured SBP.

Squirrell DM, et al. JACC Adv. 2024;3(12):101410.

SBP was significantly less reliable than the AI-predicted SBP to predict ASCVD events in people taking hypertensive medications may have important implications for the management of hypertension in clinical practice. Many of the small vessel signs of chronic hypertensive retinopathy persist even after long-term successful anti-hypertensive therapy.[19,20] The observation that the ASCVD event was highest in the lower quartile is difficult to explain. Further analysis of the demographics of individuals in the lowest and highest quartile (Supplemental Table 4) reveals that aside from SBP, the only other significant differences between the 2 groups were cholesterol medication usage, cholesterol levels, and diabetes status. As the differences in cholesterol medication usage and the corresponding cholesterol levels should have been protective, the only factor that could explain the findings was the difference in diabetes status. Further investigation revealed that more people living with diabetes in Q1 were on insulin than those in Q (3.1% vs 1.7%; P = 0.001). As insulin is a surrogate marker for high-risk diabetes, it is tempting to speculate that unexpected result we observed are explained by the finding that individuals in Q1 were not only more likely to have diabetes, but they were more likely to have high risk diabetes. The results from those individuals not on hypertension medications were less controversial. The overall ASCVD event rate increased from Q1 through Q4 regardless of whether individuals were ranked by AI-predicted or measured SBP.

There have been prior DL models designed to predict SBP from clinical data,[21] but to date, very few have attempted to predict the actual SBP from retinal images alone. Those that do report a similar MAE to ours; range 9.0 to 14.0 mm Hg.[17,22-24] It is well recognized that an individual's SBP is dependent upon multiple different physiological and methodological variables and as such, the American Heart Association guidelines recommend that the blood pressure is measured at least twice, using an appropriate cuff and device before making decisions that affect the clinical management of the patient.[25] Despite following these guidelines,[15] there was a MAE of 5.6 mm Hg in the difference between the 2 SBP readings recorded in the UKBB. As such, and because of the intrinsic physiological variation of SBP, it is arguably unrealistic to expect that the DL models predicted SBP will match the measured SBP perfectly. As such, we believe that there is an intrinsic ceiling to the performance of DL models designed to predict the measured SBP. While it may be unrealistic

to expect any DL model to replicate the actual measured SBP from a retinal image acquired with complete accuracy, the changes observed in the retinal blood vessels may better reflect an individual's long-term SBP than the measured SBP. As such, we hypothesize that the AI-predicted SBP may be a better measure of an individual's ASCVD risk than the traditional in office SBP measured on any given day.

Although UKBB followed a clinical trial protocol, there was still a variation between the 2 SBP readings and this difference had a material impact on the calculated 10-year ASCVD risk score. As the second SBP reading was typically lower than the first, 5.5% of individuals would be re-assigned to low/borderline risk (PCE $<$ 7.5%) if the second reading was used instead of the first. If the AI-predicted SBP was used to calculate the ASCVD risk, the scores were indistinguishable from those issued if the second SBP reading was used. It has been claimed that "precision medicine" is the future of cardiovascular medicine having the potential to provide a more efficient and personalized approach to the management of CVD, which differs from the traditional population-based "blanket" approach.[25] As SBP is one of the most important modifiable factors for ASCVD events, there is a pressing need to prioritize strategies to raise awareness of and screen for hypertension.[26] If the potential for preventative strategies to reduce mortality from CVD disease are to be realized, the tools and biomarkers used to predict future ASCVD risk need to be calibrated to the individual as precisely as possible. In the real-world setting of clinical medicine, precise reliable measurement of blood pressure can be difficult to achieve.[27,28] Although further work is required, our findings raise the possibility that DL models that derive their inferences from robust anatomical biomarkers could provide the precisely targeted tool required to personalize the management of CVD.

STUDY LIMITATIONS. The primary limitation of this study is that our results are based on a single dataset drawn from a largely non-Hispanic White population. Furthermore, the image quality assessment process that we employed lead to a loss of 80,123 images from 33,929 individuals. These figures represent a loss of almost 50% of the available images; or 40% of individuals, in the UKBB who had retinal images. Our study therefore represents a curated selection of individuals from the UKBB. Our claims will therefore need to be validated on other more diverse external datasets to determine whether they will generalize to broader populations. Another limitation is the UKBB only records self-reported medication usage at the time the retinal image was acquired. Consequently, we cannot know for certain that the individual was taking their medication. Finally, the accuracy of recorded ICD codes to define ASCVD events can vary. Consequently, although the UKBB validated ICD codes from hospital admissions, there may still be relevant ASCVD event data missing from the UKBB which could impact our findings.

CONCLUSIONS

AI prediction of SBP from retinal photographs across a general population was better at predicting future ASCVD events than the measured SBP. Given the variability and limitations of traditionally measured SBP, AI analysis of retinal images could potentially provide a more reliable method of deriving this biomarker and lead to more accurate ASCVD risk predictions. Further work is now required to validate our findings in other external datasets.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

D. M. S., S. Y., L. X., S. A. B., M. M., E. V., and M. V. M. are all employees of Toku Eyes. M. V. M. is also an advisor to Porter Health. Toku eyes funded this research.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A DL model, trained to predict an individual's SBP from features within a retinal image, was better correlated with subsequent ASCVD events than the in-office cuff-measured SBP.

TRANSLATIONAL OUTLOOK: Artificial intelligence analysis of the impact of SBP on the retina may better predict an individual's risk of an ASCVD event than traditional in office methods. Further research is needed to determine whether the results presented will generalize to more diverse populations.

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KEYWORDS atherosclerotic cardiovascular disease, blood pressure measurement, deep learning, retinal vasculature, systolic blood pressure

APPENDIX For the ICD codes used in this study as well as supplemental tables and a figure, please see the online version of this paper.