

Does lens opacity matter? The effect of cataract on deep learning based cardiovascular disease risk scores from fundus photos

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ABSTRACT

Purpose: To investigate the effect of cataracts on a deep learning (DL) model for cardiovascular disease (CVD) risk prediction.

Methods: This retrospective, dual-cohort study analyzed fundus images at baseline, 1, and 6-months post-cataract surgery from a longitudinal cohort (patients who underwent cataract surgery at Hanyang University Guri Hospital [HUGH]) and a cross-sectional replication cohort (Singapore Epidemiology of Eye Diseases [SEED] study). CVD risk scores were generated using an artificial intelligence (AI) software (Dr.Noan CVD). Longitudinal changes were evaluated using a generalized estimating equation (GEE) model. The association between CVD scores and cataract surgery was also assessed in the SEED study using multivariable linear regression. Subgroup analyses were performed based on diabetic retinopathy (DR) status.

Results: In the longitudinal cohort, Dr. Noon CVD scores significantly increased from baseline after cataract surgery at 1 month ($\beta = +2.14$; 95% CI, 1.28–3.01; $P < 0.001$) and 6 months ($\beta = +1.69$; 95% CI, 0.82–2.56; $P < 0.001$). A significant interaction with DR was observed, showing substantially larger score increases at 1 month (interaction $\beta = +3.02$; 95% CI, 1.20–4.85; $P = 0.001$) and 6 months (interaction $\beta = +4.78$; 95% CI, 2.99–6.56, $P < 0.001$). These findings were partially replicated in the SEED cohort, where pseudophakia was significantly associated with a higher CVD score compared to phakic eyes ($\beta = +2.60$; 95% CI, 1.71–3.49, $P < 0.001$); however, the interaction between cataract surgery and DR status was not formally significant in SEED ($P = 0.451$).

Conclusions: Cataract-induced media opacity is associated with significant attenuation of DL-derived CVD risk scores, particularly in eyes with DR. This score shift following improvement in optical clarity highlights the critical need to account for lens status when interpreting fundus-based AI prediction models.

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1. Introduction

Fundus photography has traditionally been used to detect ocular diseases including diabetic retinopathy (DR) and age-related macular degeneration.¹ More recently, it has evolved into a non-invasive “oculomics” approach, allowing quantitative assessment of retinal microvascular features such as arteriolar narrowing, venular dilation, tortuosity, and microaneurysms to predict systemic diseases like hypertension, diabetes, chronic kidney disease, and cardiovascular disease (CVD).^{2–5}

Deep learning (DL) methods have accelerated this evolution by directly leveraging standard fundus photographs to predict systemic parameters, including cardiovascular risk, without requiring additional tests.⁶ DL-based fundus models have demonstrated predictive accuracy (area under the curve up to 0.672) for five-year major adverse cardiovascular events, a modest but promising level of discrimination that, in selected studies, has compared favorably with certain traditional risk factor models, though further improvement is needed before widespread clinical adoption.^{7,8} A representative model, Dr.Noon CVD (Mediwhale Inc., Seoul, South Korea), exemplifies and extends these advances. Trained on over 200,000 fundus photographs paired with coronary artery calcium (CAC) scores measured from cardiac computer tomography (CT) scans across cohorts in South Korea, Singapore, and the United Kingdom, Dr.Noon CVD estimates CAC probability, and thus

personalized five-year CVD risk, directly from color fundus images. Its predictive performance rivals that of CT-derived CAC scoring and surpasses that of other non-invasive vascular biomarkers.⁹

However, the effect of cataract-induced media opacity on model performance has not yet been fully evaluated. Cataracts scatter incoming light, reduce image contrast, and obscure critical microvascular features necessary for accurate fundus imaging analysis.^{10,11} Simulated cataract has been shown to markedly degrade the diagnostic performance of deep learning models for diabetic retinopathy detection¹², suggesting that lens opacity may likewise impair DL-based cardiovascular risk prediction. Because cataracts are prevalent in older adults—a population at elevated cardiovascular risk—the extent to which cataract-related opacity affects DL-derived cardiovascular scores, and whether such attenuation has clinically meaningful implications for cardiovascular risk prediction, remains unclear.

Therefore, this study aimed to evaluate the impact of cataract-induced media opacity on cardiovascular risk scores (ie. Dr.Noon CVD) derived from fundus photography in two independent cohorts from Korea and Singapore.

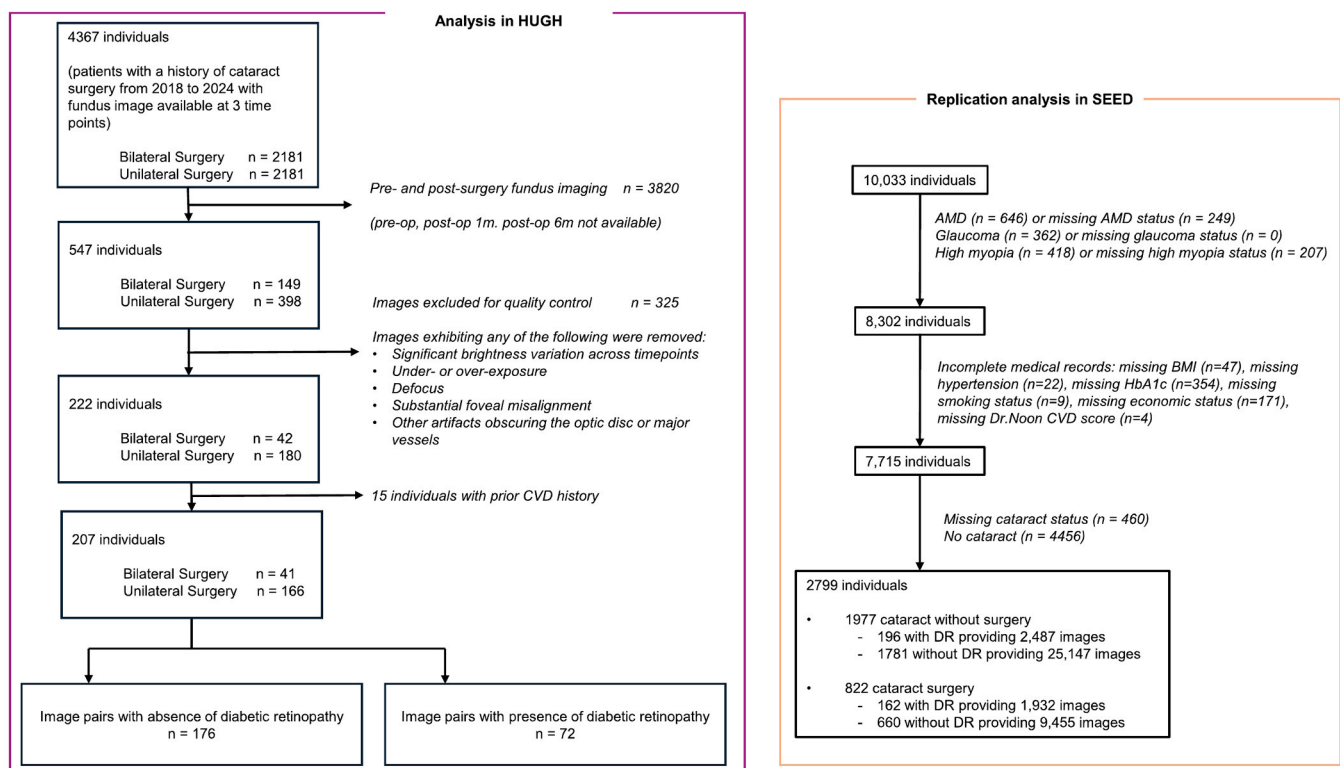


Fig. 1. Participant Enrolment and Utilization of Bilateral Eye Images for Independent Analysis (Inclusion and exclusion criteria for the study population). A total of 4367 patients who underwent cataract surgery at Hanyang University Guri Hospital between January 2018 and December 2024 were initially enrolled, and fundus images were available at three time points (preoperatively, 1 month postoperatively, and 6 months postoperatively). Patients with missing images were excluded (n = 3820), leaving 547 eligible patients. Additional exclusions were made based on image quality issues, including significant brightness variations across time points, under- or over-exposure, defocus, substantial foveal misalignment, and other artifacts obscuring the optic disc or major vessels (n = 325). After applying all criteria, 207 patients remained eligible for the analysis. Among them, bilateral surgery cases with only one eye meeting the inclusion criteria were reclassified as unilateral cases, resulting in 41 bilateral and 166 unilateral cases. For bilateral cases, each eye was analyzed separately, yielding 248 image pairs for assessment. Postoperative images were reviewed for the presence of DR. For the replication analysis in the Singapore Epidemiology of Eye Diseases (SEED) cohort, 10,033 individuals were screened. Participants with age-related macular degeneration, glaucoma, or high myopia (including those with missing status for these conditions) were excluded (n = 1731), leaving 8302 individuals. Of these, 587 subjects with incomplete medical records were excluded, leaving 7715 individuals. Finally, after excluding those with missing cataract status or no cataract (n = 4916), 2799 individuals were included: 1977 with cataracts but no history of surgery (196 with DR providing 2487 images; 1781 without DR providing 25,147 images), and 822 with a history of cataract surgery (162 with DR providing 1931 images; 660 without DR providing 9455 images).

2. Methods

2.1. Study population and exclusion criteria (Fig. 1)

The Hanyang University Guri Hospital (HUGH) cohort is a single hospital-based longitudinal cohort comprised of consecutive patients who underwent routine cataract surgery at HUGH between January 2018 and December 2024. To be eligible, each patient was required to have gradable fundus photographs at three standardized time points (preoperative baseline and post-operative (op) 1 and 6 months). Eyes were excluded if any fundus photograph at each time point was missing, if there was prior intraocular surgery (other than cataract surgery), or if media opacity other than cataract (e.g., corneal opacity, vitreous hemorrhage, or vitreous opacity) was present. Eyes were also excluded if fundus photographs failed to meet the quality standards (detailed criteria in the Image Quality Assessment section below). Finally, patients with a history of CVD were excluded. In bilateral cases, both eyes were included if each met all criteria; otherwise, only qualifying eyes were included (Fig. 1.) The final sample represented a longitudinal dataset that allowed the within-eye assessment of Dr.Noon CVD score changes following cataract surgery. The Institutional Review Board of Hanyang Guri Hospital approved this study (IRB No. 2024-12-007-001), which adhered to the principles outlined in the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of this study.

The replication analysis was conducted within the Singapore Epidemiology of Eye Diseases (SEED) study, which collected data from 2004 to 2011 using population-based sampling among three major ethnic groups: Malay, Indian, and Chinese and included 10,033 adults aged 40–86 years.¹³ A total of 146,096 retinal images were collected from 10,033 initially included participants. Same As with HUGH cohort, we excluded 1481 (1.0%) that does not meet the image quality criteria, leaving 144,615 gradable images from 10,033 patients. Of these, those with ocular comorbidities known to affect fundus appearance (specifically age-related macular degeneration, glaucoma, or high myopia), or those with unknown disease status for these conditions, were excluded ($n = 1731$). We also excluded 587 subjects with incomplete information on body mass index (BMI), hypertension, HbA1c, smoking status, economic status, or Dr.Noon CVD score. Among the remaining 7715 individuals we retained only those with either (1) clinically diagnosed cataract without prior cataract surgery ($n = 1977$, 196 with DR providing 2487, 1781 without DR providing 25,147 images) or (2) a history of cataract surgery ($n = 822$, 162 with DR providing 1931 images, 660 without DR providing 9455 images).

2.2. Data collection

Demographic and clinical data of patients were extracted from HUGH electronic medical records, including age and sex. Lens opacity was graded on slit-lamp examination using the Lens Opacities Classification System III¹⁴, recording the cortical (C), nuclear (NC), and posterior subcapsular (P) opacities in each eye. Nuclear Opalescence (NO) was not assessed in this study. All patients received the TECNIS® Monofocal 1-Piece IOL (Model ZCB00; Johnson & Johnson Vision, Santa Ana, CA, USA), a single-piece UV-blocking hydrophobic acrylic IOL without blue-light chromatic filtering, ensuring uniformity of IOL type across the cohort.

In the SEED cohort, demographic, systemic, and ocular data were collected using standardized interviewer-administered questionnaires, clinical examinations, and fundus and lens photography. Lens opacities were graded from lens photographs using the Wisconsin Cataract Grading System.¹⁵

2.3. Fundus image acquisition

Color fundus photographs from HUGH were obtained by a single,

skilled examiner using a Topcon DRI optical coherence tomography (OCT) device (Topcon Corporation, Tokyo, Japan) without pupil dilation. The images were then converted to digital imaging and communications in medicine format for subsequent analysis.

Color fundus photographs from SEED were obtained using a Canon CR-1 Mark-II non-mydiatic retinal camera (Canon Inc., Tokyo, Japan) after pupil dilation.

2.4. Image quality assessment

All images retained in the HUGH cohort were subjected to manual quality control. Photographs with excessive brightness variation across time points, under- or over-exposure, defocus, substantial foveal displacement, or artifacts obscuring the optic disc or major retinal vessels were excluded. Two quantitative image-quality metrics were computed for the remaining images. The first was the quality score (QS), an internally generated score from the Dr.Noon CVD algorithm, where lower values reflect clearer images with fewer artifacts. The second was the image quality (IQ) index, a proprietary metric provided by Topcon, in which higher values indicate better overall image quality. Both QS and IQ ranged from 0 to 100, with no additional numeric thresholds applied beyond the manual visibility criteria.

2.5. Dr.Noon CVD score

Dr.Noon CVD is an AI-based, DL-driven software that estimates five-year CVD risk by analyzing retinal images using a convolutional neural network (CNN). As illustrated in the workflow (Supplementary figure 1), the system first acquires color fundus photographs, which are then processed through a series of convolutional layers for feature extraction. These extracted features are ultimately converted into a single output: the Dr.Noon CVD score, a numerical value from 0 to 100. In this study, all reported scores are presented to two decimal places for consistency. Technical information about Dr.Noon is already well illustrated in existing research at the development stage.⁹

This CNN was trained using a large dataset of retinal images paired with CAC measurements, allowing the model to learn retinal signatures that correlate with subclinical atherosclerosis. After processing the image, the software provides a quantitative five-year CVD risk estimate, categorizing patients into low (<1% risk, corresponding to scores <30.93), moderate (1–5% risk, 30.93–40.74), or high (>5% risk, >40.74). Consequently, Dr.Noon CVD offers a clinician-friendly and objective measure of future CVD risk based on subtle vascular and structural features visible in fundus photographs.

2.6. Dr.Noon CVD saliency maps

To visualize the model's decision-making process, we generated saliency maps for representative fundus images.¹⁶ A saliency map is computed by taking the gradient of the model's output to the corresponding input image pixels. The gradient indicates how sensitive the model prediction is to small changes in each pixel. Larger absolute gradient values correspond to pixels that contribute more strongly to the model's decision.

2.7. Diabetic retinopathy grading

DR is highly prevalent in the study population and can substantially modify fundus image characteristics—such as contrast, reflectance, and lesion-related textures (hemorrhages, exudates, or laser scars)—independent of cataract-induced media opacity. Consequently, an equivalent degree of opacity-related image degradation may have differential effects on the availability and reliability of model-relevant retinal signals in eyes with versus without DR. We therefore evaluated DR as a clinically meaningful effect modifier to improve interpretability and to account for potential heterogeneity in the relationship between media

opacity and the AI-derived outcome.

To evaluate the effect of DR on DL-based cardiovascular predictions, participants were stratified based on the presence or absence of DR. In the HUGH cohort, DR status was determined by two retinal specialists (Y.U.S. and S.H.) who independently reviewed the fundus photographs to determine the presence or absence of diabetic retinopathy according to the International Clinical Diabetic Retinopathy (ICDR) Severity Scale.¹⁶ As DR was classified as binary (present or absent), Cohen's kappa was used to assess interobserver agreement, which was excellent ($\kappa > 0.9$).

In the SEED cohort, the presence of DR was centrally graded using standardized classification systems as part of the original study design. Grading was performed by trained personnel using protocols based on the modified Airlie House.^{17–19}

2.8. Statistical analysis

All statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing), with statistical significance set at $P < 0.05$.

In the HUGH cohort, longitudinal changes in Dr.Noon CVD score, QS, and IQ were evaluated at the eye level across three time points (baseline, 1-month post-op, and 6-months post-op) were assessed. We used the Friedman test for overall comparisons, followed by pairwise paired *t*-tests (for Dr.Noon CVD score) or Wilcoxon signed-rank tests (for QS and IQ), with Holm's adjustment for multiple comparisons. To account for potential confounders (age, sex, and DR) and the correlation between repeated measurements within the same eye, and the potential correlation between fellow eyes from the same patient in bilateral cases, we used a generalized estimating equation (GEE) model with patient as the clustering unit. This approach treats all observations from the same patient—across both eyes and time points—as correlated, thereby addressing both levels of dependency simultaneously.

In the SEED cohort, Dr.Noon CVD scores were first computed for all available retinal images per participant. Images failing to meet the pre-specified quality control criteria were excluded. For participants with multiple gradable images, including images from both eyes where available, all remaining scores were averaged to yield a single participant-level CVD score, which served as the outcome variable in the multivariable linear regression analysis. Specifically, we compared individuals with clinically diagnosed cataract without prior surgery and those with a history of cataract surgery. The model was adjusted for a comprehensive set of confounding factors: age, sex, ethnicity, BMI, HbA1c, hypertension, smoking status, socioeconomic status, and DR. We also performed a stratification analysis according to DR status and tested the possible interaction between cataract surgery and DR in the regression model.

3. Results

3.1. Baseline characteristics

A total of 248 eyes from 207 patients were included in the HUGH cohort. Of these, 72 eyes had DR and 176 did not. The overall mean age was 68.79 ± 8.82 years, and 110 (44.35%) of the participants were male. Individuals with DR were significantly younger than those without (65.12 ± 10.02 vs. 70.28 ± 7.83 years, $P < 0.001$). Moreover, the baseline IQ score was 81.42 ± 12.52 in the DR group versus 83.46 ± 14.28 in the group without ($P = 0.077$). The baseline QS score was 57.44 ± 30.77 versus 54.72 ± 29.04 ($P = 0.551$), and the baseline Dr.Noon CVD score was 47.89 ± 7.87 versus 47.26 ± 7.91 ($P = 0.572$). The detailed characteristics are summarized in Table 1. There was no significant difference in the mean scores for cortical opacity (1.42 ± 1.25 vs. 1.22 ± 1.30 , respectively; $P = 0.278$) or nuclear sclerosis (2.72 ± 0.83 vs. 2.84 ± 0.75 ; $P = 0.316$) between the eyes with and without DR. However, the posterior subcapsular opacity (P) score was

Table 1

Demographic and clinical characteristics of participants, stratified by the presence of diabetic retinopathy.

	Overall (n = 248 eyes)	Eyes with DR (n = 72 eyes)	Eyes without DR (n = 176 eyes)	P value
Age (years)	68.79 ± 8.82	65.12 ± 10.02	70.28 ± 7.83	< 0.001 ²
Sex (male, %)	110 (44.35)	35 (48.61)	75 (42.61)	0.273 ¹
Laterality (Right, %)	119 (47.98)	35 (48.61)	84 (47.73)	1.000 ¹
IQ				
Baseline	82.87 ± 13.80	81.42 ± 12.52	83.46 ± 14.28	0.077 ²
Post-op 1 m	89.13 ± 8.97	87.01 ± 9.05	89.99 ± 8.82	0.006 ²
Post-op 6 m	90.29 ± 7.06	88.75 ± 6.12	90.92 ± 7.33	< 0.001 ²
QS				
Baseline	55.51 ± 29.52	57.44 ± 30.77	54.72 ± 29.04	0.551 ²
Post-op 1 m	29.54 ± 29.56	38.45 ± 31.48	25.89 ± 28.02	0.002 ²
Post-op 6 m	25.64 ± 26.67	31.64 ± 29.22	23.19 ± 25.24	0.035 ²
Dr.Noon CVD score				
Baseline	47.44 ± 7.88	47.89 ± 7.87	47.26 ± 7.91	0.572 ³
Post-op 1 m	49.59 ± 9.31	52.17 ± 9.70	48.53 ± 8.96	0.007 ³
Post-op 6 m	49.13 ± 9.26	52.97 ± 9.59	47.57 ± 8.67	< 0.001 ³

Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as n (%).

DR, diabetic retinopathy; IQ, image quality score from Topcon; QS, image quality score from Dr.Noon CVD

1 Chi-square test

2 Wilcoxon rank-sum

3 Two-sample *t*-test

$P < 0.05$ as statistically significant

Table 1 summarizes the demographic characteristics, image quality metrics, and Dr.Noon CVD scores for the overall cohort (n = 248 eyes) and for the subgroups with and without diabetic retinopathy (DR). The mean age was 68.79 ± 8.82 years, with no significant sex or laterality differences between DR and non-DR groups. In the overall cohort, image quality improved significantly after cataract surgery, as indicated by the increased IQ scores and decreased QS scores from baseline to postoperative visits. Dr.Noon CVD scores also showed a modest postoperative increase across the entire sample. Subgroup analysis revealed that while baseline image quality and CVD scores were comparable between the DR and non-DR groups, postoperative IQ remained significantly lower and QS was significantly higher in eyes with DR, reflecting persistent image degradation, likely due to retinal pathology. Notably, the DR group also demonstrated a greater increase in Dr.Noon CVD scores after surgery despite similar baseline values, suggesting the unmasking of high-risk retinal features after media opacity removal.

significantly higher in the group with DR compared to those without (0.74 ± 1.28 vs. 0.37 ± 0.82 ; $P = 0.023$) (Supplementary Figure 2). Upon systematic chart review of all 248 included eyes, posterior capsule opacification (PCO) requiring Nd:YAG laser posterior capsulotomy developed in 7 eyes (2.8%) between the 1-month and 6-month post-operative visits; in all cases, 6-month fundus images were acquired after confirmed resolution of PCO-related opacity. Post-operative cystoid macular edema (CME) occurred in 6 eyes (2.4%), all of which resolved fully with treatment prior to image acquisition. No eye had active PCO or CME at any of the three imaging time points.

The baseline characteristics of the 2799 participants in the SEED cohort are summarized in Table 2. The mean age of this population was 65.7 ± 8.4 years, and it was composed of three major ethnic groups (Chinese, 31.4%; Indian, 32.8%; Malay, 35.8%). Within this cohort, 1977 (70.6%) participants were cataractous and 822 (29.4%) were pseudophakic.

Table 2
Demographic and clinical characteristics of participants in the SEED cohort.

Characteristic	Overall (n = 2799)
Cataract status, (%)	
Cataractous	1977 (70.6)
Pseudophakic	822 (29.4)
Age (years)	65.7 ± 8.4
Sex (male, %)	1387 (49.6)
Ethnicity, (%)	
Chinese	876 (31.3)
Indian	916 (32.7)
Malay	1007 (36)
BMI (kg/m ²)	25.4 ± 4.7
HbA1c (%)	6.5 ± 1.5
Hypertension, (%)	2211 (79)
Smoking status (%)	
Never	1900 (67.9)
Current	402 (14.4)
Past	497 (17.8)
Low SES (%)	230 (8.2)

Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as n (%).

BMI, body mass index; SES, socioeconomic status.

Table 2 summarizes the demographic and clinical characteristics for the overall SEED cohort (n = 2799). The cohort consisted of individuals with cataracts who had not undergone surgery (70.6%) and those who were pseudophakic (29.4%). The mean age was 65.7 ± 8.4 years. The cohort was composed of three major ethnic groups (Chinese, 31.4%; Indian, 32.8%; Malay, 35.8%), and the prevalence of hypertension was 79.0%.

3.2. Postoperative changes in image quality

In HUGH cohort, image quality factors improved substantially after cataract surgery; QS, where lower values indicate better clarity, decreased significantly over time, while the IQ, where higher values indicate better quality, increased (Supplementary Figure 3). These improvements were most prominent at post-op 1 month and were sustained through post-op 6 months (Supplementary Figure 2 and Supplementary Table 2).

3.3. Postoperative changes in Dr.Noon CVD score in HUGH cohort

In the overall cohort, the median Dr.Noon CVD score increased significantly from 48.14 (IQR: 42.19–52.98) at baseline to 50.34 (IQR: 43.70–55.93) at post-op 1 month, with a slight decline to 49.38 (IQR: 43.85–54.68) at post-op 6 months (Friedman $P < 0.001$). These values

are not included in the test-retest repeatability range of the Dr.Noon CVD score²⁰, and significant differences were observed between baseline and post-op 1 month ($P < 0.001$) and between baseline and post-op 6 months ($P < 0.001$), whereas the change from 1 month to 6 months was not significant ($P = 0.310$) (Fig. 2 and Supplementary Table 3).

After adjusting for possible confounders (GEE model), the Dr.Noon CVD score significantly increased from baseline by 2.14 points [95% confidence interval (CI), 1.28–3.01; $P < 0.001$] at post-op 1 month and by 1.69 points (95% CI, 0.82–2.56; $P < 0.001$) at post-op 6 months (Table 3). Other factors significantly associated with a higher score were older age ($\beta = 0.29$ per year; 95% CI, 0.18–0.40; $P < 0.001$), male sex ($\beta = 4.55$; 95% CI, 2.80–6.29; $P < 0.001$), and the presence of DR ($\beta = 4.44$; 95% CI, 2.62–6.26; $P < 0.001$).

To assess the clinical magnitude of these score changes, we examined risk category reclassification before and after surgery. At baseline, the majority of patients were already classified as high risk (166/207, 80.2%), limiting the potential for upward reclassification. At 1 month post-operatively, 19 patients (9.2%) migrated to a higher risk category and 16 (7.7%) to a lower category; at 6 months, 21 (10.1%) migrated upward and 15 (7.2%) downward. The most clinically relevant transition (from moderate to high risk, potentially prompting changes in preventive management) occurred in 14 patients (6.8%) at 1 month and 15 patients (7.2%) at 6 months.

3.4. Synergic effect of cataract and DR status on Dr.Noon CVD score

The effect of cataract surgery on CVD scores differed according to the DR status. In eyes with DR, the median Dr.Noon CVD score increased from 49.64 (IQR: 41.95–53.22) at baseline to 53.25 (IQR: 46.93–58.07) at post-op 1 month and 52.98 (IQR: 46.41–59.17) at post-op 6 months (Friedman $P < 0.001$) (Supplementary Table 3). Improvements from baseline to both postoperative time points were significant ($P < 0.001$), with no significant changes between post-op 1 and 6 months ($P = 0.270$).

In contrast, eyes without DR showed no significant changes (Friedman test, $P = 0.059$). The median score was 47.74 (IQR: 42.28–52.85) at baseline, 49.71 (IQR: 42.36–54.26) at post-op 1 month, and 47.51 (IQR: 42.80–53.26) at post-op 6 months, with only the increase from baseline to post-op 1 month reaching significance ($P = 0.028$), while changes at post-op 6 months were not significant ($P = 0.349$ vs. baseline; $P = 0.117$ between 1 and 6 months).

We tested for an interaction between cataract surgery and DR status, while adjusting for potential confounders (Table 3). The interaction coefficients confirmed significantly greater score increases in DR eyes compared to non-DR eyes: + 3.02 points (95% CI, 1.20–4.85;

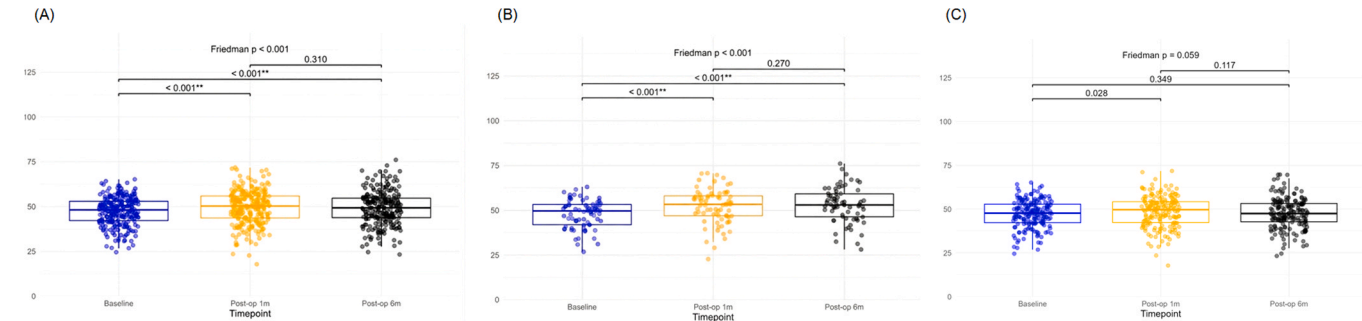


Fig. 2. Longitudinal changes in Dr.Noon CVD score at baseline, 1 month, and 6 months post-operation in (A) all eyes (n = 248), (B) eyes with diabetic retinopathy (n = 72), and (C) eyes without diabetic retinopathy (n = 176). Boxplots show median, interquartile range, and whiskers (1.5 × IQR), with individual data points overlaid. Overall differences across time points were assessed by the Friedman test; pairwise comparisons were made with Holm-adjusted paired t -tests. In the overall cohort (Fig. 2A), Dr.Noon CVD scores increased significantly from baseline to 1 month and from baseline to 6 months (both $P < 0.001$), with no significant difference between 1 and 6 months ($P = 0.310$). In eyes with diabetic retinopathy (Fig. 2B), similar significant increases were observed from baseline to 1 and 6 months (both $P < 0.001$), with no significant difference between 1 and 6 months ($P = 0.270$). In eyes without diabetic retinopathy (Fig. 2C), the Friedman test result was borderline ($P = 0.059$). Pairwise analysis showed a significant increase from baseline to 1 month ($P = 0.028$), whereas the increases from baseline to 6 months ($P = 0.349$) and 1 month to 6 months ($P = 0.117$) were not significant.

Table 3

GEE model estimates for the Dr.Noon CVD score in the HUGH cohort: overall, interaction model, and stratification by diabetic retinopathy (DR) status.

Predictor	Overall		DR		No DR	
	β (95% CI)	p-value	β (95% CI)	P value	β (95% CI)	P value
Post-op 1 m vs. Baseline	2.14 (1.28, 3.01)	< 0.001	4.29 (2.78–5.80)	< 0.001	1.26 (0.24–2.23)	0.016
Post-op 6 m vs. Baseline	1.69 (0.82, 2.56)	< 0.001	5.08 (3.59–6.57)	< 0.001	0.30 (–0.69–1.30)	0.548
Age (per year)	0.29 (0.18, 0.40)	< 0.001	0.37 (0.21–0.54)	< 0.001	0.23 (0.09–0.37)	0.001
Gender (male vs. female)	4.55 (2.80, 6.29)	< 0.001	5.80 (2.65–8.93)	< 0.001	3.96 (1.87–6.05)	< 0.001
DR (yes vs. no)	4.44 (2.62, 6.26)	< 0.001	—	—	—	—
Interaction terms						
Post-op 1 m $\times$ DR	3.02 (1.20, 4.85)	0.001	—	—	—	—
Post-op 6 m $\times$ DR	4.78 (2.99, 6.56)	< 0.001	—	—	—	—

Postoperative timepoint was modeled as a categorical variable, with baseline as the reference.

Age was modeled per year; β represents the change in score per 1-year increase.

The sex was coded as male or female (reference).

DR: Diabetic retinopathy status (yes vs. no [reference]).

The interaction terms between the postoperative time point and DR were assessed in a separate model to evaluate the effect modification.

Stratified models were constructed separately for eyes with and without DR, excluding DR status from the covariates.

β values are regression coefficients with 95% confidence intervals (CI); p-values are from Wald *t*-tests.

Statistical significance was defined as $p < 0.05$.

Abbreviations: β , regression coefficient; CI, confidence interval; DR, diabetic retinopathy.

This table summarizes the GEE model results estimating the effect of cataract surgery on Dr.Noon CVD scores, both overall and stratified by DR status. In the overall model, Dr.Noon CVD scores significantly increased at both 1 and 6 months postoperatively compared with baseline. Older age, male sex, and presence of DR were independently associated with higher scores. Stratified models showed a markedly greater score increase in eyes with DR, particularly at 6 months, whereas the increase in non-DR eyes was smaller and not statistically significant at 6 months. The interaction terms confirmed a significant effect of DR, indicating that the impact of cataract surgery on the AI-based risk score was amplified in the presence of retinal pathology.

$P = 0.001$) at post-op 1 month and + 4.78 points (95% CI, 2.99–6.56; $P < 0.001$) at post-op 6 months.

3.5. Visualization of AI model focus with saliency maps

To provide a mechanistic explanation for the observed score changes, we analyzed representative cases using saliency maps (Fig. 3). A significant shift in the model's saliency map patterns was observed following cataract surgery. Preoperatively, cataract-induced opacity restricted the field of view, causing the model's attention signals to

concentrate on non-specific features around the visible optic disc. However, after cataract surgery, the improved clarity across the entire fundus allowed the model to assign stronger signals to regions corresponding to features associated with established cardiovascular risk markers—such as thin retinal arterioles, hemorrhages, and hard exudates—that were previously unobservable or partially obscured. This shift in model attention toward features associated with established retinal risk markers is consistent with, though does not confirm, an unmasking of underlying pathology as the mechanism driving the higher Dr.Noon CVD scores postoperatively.

3.6. Replication in SEED cohort

The analyses performed in SEED cohort confirmed that cataract surgery was significantly associated with a higher Dr.Noon CVD score ($\beta = 2.60$; 95% CI, 1.71–3.49; $P < 0.001$) (Table 4). Moreover, consistent with the primary analysis, the presence of DR was also a strong predictor of a higher score ($\beta = 12.83$; 95% CI, 11.25–14.41; $P < 0.001$). Regarding the potential interaction between cataract surgery and DR, the formal interaction term was not statistically significant ($P = 0.451$), indicating that effect modification by DR status was not formally established in the SEED cohort. In stratified analyses, the effect of cataract surgery was statistically significant in both the DR subgroup ($\beta = 5.03$; 95% CI, 2.83–7.23; $P < 0.001$) and the non-DR subgroup ($\beta = 2.29$; 95% CI, 1.32–3.26; $P < 0.001$). While the point estimate was numerically larger in the DR subgroup, this difference was not formally supported by the interaction test and should be regarded as hypothesis-generating only.

4. Discussion

In this study, we demonstrated that AI-derived CVD risk scoring software that uses fundus photographs predicts a higher CVD risk score after cataract surgery than before surgery. This finding was consistent across both longitudinal hospital-based and a large-scale population-based cohort, underscoring the robustness of this observation. The increase in the CVD risk score was particularly pronounced in patients with DR.

The observed postoperative elevation in CVD scores is most consistent with, though not conclusively proven to represent, an ‘unmasking’

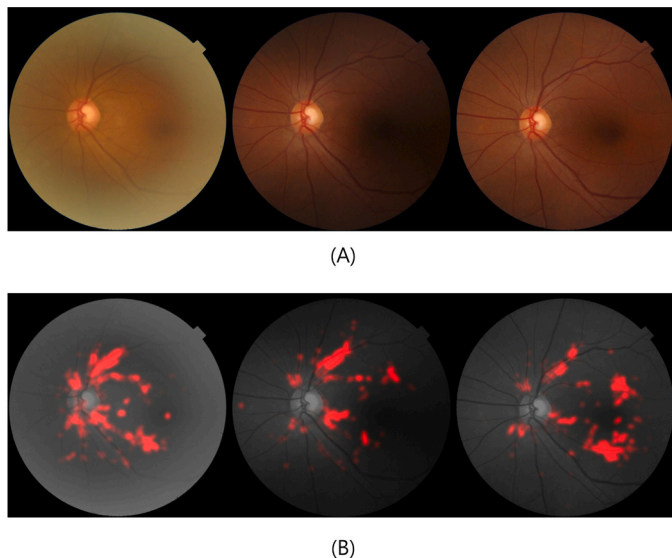


Fig. 3. Unmasking of Retinal Features and Shift in AI Model Attention After Cataract Surgery in Representative Eyes Without Diabetic Retinopathy (DR). A representative eye without DR. The series of fundus photographs (A) and corresponding saliency maps (B) are shown preoperatively, at 1-month post-op, and at 6-months post-op. The Dr.Noon CVD scores were 49.56, 39.89, and 37.89, respectively. The preoperative saliency map shows attention focused around the optic disc, which shifts to other retinal areas after surgery improves image clarity.

Table 4.

Linear Regression Model Estimates for Dr.Noon CVD Score in the SEED Cohort, Overall and Stratified by Diabetic Retinopathy Status.

Predictor	Overall (n = 2799)		DR (n = 358)		No DR (n = 2441)	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
Cataract surgery (yes vs. no)	2.60 (1.71, 3.49)	< 0.001	5.03 (2.83, 7.23)	< 0.001	2.29 (1.32, 3.26)	< 0.001
Age (per year)	1.13 (1.08, 1.18)	< 0.001	0.86 (0.72, 1.01)	< 0.001	1.16 (1.11, 1.22)	< 0.001
Gender (male vs. female)	-15.72 (-16.69, -14.76)	< 0.001	-14.38 (-17.11, -11.66)	< 0.001	-15.83 (-16.86, -14.8)	< 0.001
Ethnicity (ref = Chinese)						
Indian	4.31 (3.33, 5.29)	< 0.001	2.11 (-0.71, 4.94)	0.142	4.47 (3.42, 5.53)	< 0.001
Malay	5.52 (4.52, 6.51)	< 0.001	2.96 (-0.29, 6.21)	0.074	5.72 (4.68, 6.76)	< 0.001
BMI (per kg/m ²)	0.36 (0.28, 0.45)	< 0.001	0.15 (-0.06, 0.37)	0.161	0.39 (0.29, 0.48)	< 0.001
HbA1c (per %)	2.44 (2.15, 2.74)	< 0.001	1.43 (0.85, 2.00)	< 0.001	2.70 (2.35, 3.05)	< 0.001
Hypertension (yes vs. no)	4.93 (3.93, 5.94)	< 0.001	6.53 (3.18, 9.88)	< 0.001	4.57 (3.51, 5.62)	< 0.001
Smoking (ref = Never)						
Former	1.07 (-0.22, 2.35)	0.104	-2.76 (-6.42, 0.91)	0.141	1.48 (0.11, 2.85)	0.034
Current	0.07 (-1.13, 1.27)	0.911	0.91 (-2.32, 4.13)	0.581	-0.12 (-1.40, 1.17)	0.856
Low SES (yes vs. no)	-1.1 (-2.53, 0.32)	0.129	-0.43 (-3.74, 2.88)	0.8	-1.27 (-2.83, 0.30)	0.113
DR (yes vs. no)	8.78 (7.50, 10.07)	< 0.001	—	—	—	—

Linear regression models were fitted for the overall cohort and stratified according to DR status.

The overall model included cataract surgery status, age, sex, ethnicity, BMI, HbA1c level, hypertension, smoking status, socioeconomic status (SES), and diabetic retinopathy (DR) as covariates.

Stratified models used the same covariates but omitted DR status.

β values are regression coefficients with 95% confidence intervals (CI); p-values are from *t*-tests.

Reference categories: no cataract surgery, female sex, Chinese ethnicity, never smoker, no hypertension, no low SES, and (for the overall model) no DR.

Age and BMI were modeled per unit, and HbA1c was modeled per 1% increase.

Statistical significance was set at $p < 0.05$.

BMI, body mass index; HbA1c, glycated hemoglobin; SES, socioeconomic status; DR, diabetic retinopathy; CI, confidence interval.

This table presents the multivariable linear regression results assessing the association between cataract surgery and Dr.Noon CVD scores in the overall SEED cohort as well as in stratified subgroups with and without diabetic retinopathy (DR). In the overall model, cataract surgery was independently associated with significantly higher CVD scores, after adjusting for demographic and clinical covariates. Stratified analyses revealed that this association was evident in both the DR and non-DR subgroups. The effect estimate was numerically larger in the DR subgroup ($\beta=5.03$; 95% CI, 2.83–7.23) than in the non-DR subgroup ($\beta=2.29$; 95% CI, 1.32–3.26). The interaction term between cataract surgery and DR status was not statistically significant, suggesting no formal evidence of effect modification. Other significant predictors included age, male sex, Malay and Indian ethnicities, higher BMI, elevated HbA1c levels, and hypertension.

of pre-existing retinal pathology following improvement in optical clarity. An alternative explanation that IOL-related changes in chromatic filtering, image brightness, or pseudophakic optical properties generate a spurious upward signal, cannot be excluded without outcome-linked validation data. This interpretation is supported by two lines of evidence from our data. First, we documented a significant improvement in fundus image quality postoperatively, as evidenced by increases in the Topcon IQ and decreases in the Dr.Noon QS. Second, this aligns with external evidence from imaging studies, such as OCT angiography, which shows that in the pseudophakic eye, retinal vessel density and perfusion can be captured with significantly greater precision.^{21,22} By clearing the optical media, the induction of pseudophakia unmasks well-established cardiovascular biomarkers such as microvascular architecture (vessel caliber, tortuosity)²³, focal lesions (microaneurysms, hemorrhages)²⁴, and neuro-retinal structural changes (RNFL thinning)^{25–27}, more visible to the AI algorithm. In addition, the human lens accumulates yellow chromophores with age and progress nuclear sclerosis, which increases the absorption of short-wavelength (blue and green) light²⁸, and cataract acts as a yellow filter when taking fundus photographs. Therefore, cataract surgery not only unmasks physical features, but also fundamentally changes the color information available to the AI.

However, because the Dr. Noon CVD score is derived from an integrated analysis of multiple retinal features^{29,30}, although post-operatively media clarity improvement enhanced overall fundus contrast, color fidelity, and the visibility of fine structural details — thereby increasing the amount of retinal signals available to the AI model (including vascular and background features)—the present study could not determine which specific lesions or features (e.g., retinal vascular caliber, hemorrhages, exudates)^{31,32}, primarily drove the observed increase in scores. This issue should be clarified through further analyses in future investigations.

In our study, the CVD scores between patients with and without DR were statistically similar before surgery ($P = 0.572$) but became

distinctly different after surgery, with the DR group showing a significantly greater increase (post-op 1 month $P = 0.007$, post-op 6 months $P < 0.001$). This supports the interpretation that surgery unmasks the underlying pathology. DR is a well-established and powerful risk factor for cardiovascular events, with risk increasing with severity; meta-analyses report that while any DR is associated with a relative risk (RR) for incident CVD of up to 2.42, this risk stratifies from an RR of 1.38 for non-proliferative DR (NPDR) to 2.32 for proliferative DR (PDR).^{33,34} Our GEE model provides a quantitative measure of the clinical significance of this effect, showing that in patients with DR, pseudophakia was associated with an increase in CVD score of 4.29 and 5.08 points at 1 and 6 months postoperatively, respectively. Given an age-related coefficient of 0.37 per year in the DR stratum, this score increment corresponds arithmetically to approximately 12–14 years' worth of age-associated score accumulation within the model. This comparison is intended to contextualize the magnitude of the coefficient and should not be interpreted as biological equivalence to aging, as the model coefficient reflects learned statistical associations rather than a causal physiological trajectory. This trend was directionally consistent in the SEED cohort, though the formal interaction term between cataract surgery and DR did not reach statistical significance in that cohort ($P = 0.451$). This discrepancy likely reflects differences in study design—SEED's cross-sectional comparison lacks the within-subject precision of HUGH's longitudinal approach—as well as the smaller DR subgroup in SEED ($n = 358$), which may have limited statistical power to detect a significant interaction. Differences in DR severity distribution and camera-related image characteristics between cohorts may also have contributed. The SEED stratified results are therefore presented as directionally consistent but formally unconfirmed.

This observed pattern raises a critical question and addresses the "black box" problem in medical AI. Is the score increase driven by the model detecting biologically meaningful features or simply by improved image clarity? After undergoing cataract operation, the AI model could clearly visualize the features of DR, such as microaneurysms,

hemorrhages, and hard exudates, which are established markers of systemic cardiovascular risk.^{35,36} Our saliency map analysis provides observational evidence consistent with, but not confirming, this mechanism; saliency maps indicate which image regions influence model output but cannot establish that those regions correspond to biologically validated cardiovascular biomarkers. Preoperatively, the model's attention was concentrated around the optic disc, but postoperatively, the map's activation shifted to become highly specific, selectively highlighting the pathological signals that drive elevated Dr.Noon CVD scores. Because retinal microvascular changes are known surrogates of systemic vascular health, it is presumed that AI models learn to detect these features. Our finding that the score increased most significantly when DR was unmasked is consistent with this principle, though it does not constitute direct biological validation. Published saliency maps from the development of the Dr.Noon CVD model offer computational insights, indicating that the model strongly highlights the retinal vessels.⁹ Our "natural experiment" therefore complements other computational explainable AI techniques like SHAP (SHapley Additive exPlanations)³⁷ and Gradient-weighted Class Activation Mapping (Grad-CAM)³⁸ by providing real-world corroborating evidence that warrants further mechanistic investigation. This supports the biological plausibility of the model's behavior, suggesting that its predictive power may be grounded in the detection of clinically established features rather than abstract patterns—a hypothesis-generating insight that warrants confirmation through controlled feature-level experiments and prospective outcome validation, but which nonetheless offers an encouraging basis for building clinical trust.

To address the clinical challenge of systematically altered risk score output in cataractous eyes—evidenced by a moderate-to-high risk category transition in 6.8–7.2% of patients following surgery, a threshold with direct implications for preventive decisions such as statin initiation—whether representing true underestimation or an optical artifact, and to maximize clinical utility, future iterations of this software should be enhanced in two ways. First, there is a critical need to improve the model transparency. Incorporating explainable AI techniques such as SHAP³⁷ and Grad-CAM³⁸ would allow clinicians to precisely determine which retinal features contribute to a given score, thus increasing diagnostic confidence. Second, the software should integrate an internal module that quantifies and compensates for media opacity, which is a well-established principle in clinical ophthalmology. For example, a signal-to-noise ratio (SNR) below 2.0 alerts clinicians to a potential hyperopic bias in axial length readings, often prompting a compensatory adjustment in IOL power.^{10,11} Similarly, a high standard deviation in OCT-based central corneal thickness measurements can indicate poor tear film quality, leading to an underestimation of pachymetry.³⁹ Therefore, future AI software should integrate analogous quality assessment metrics to flag or even dynamically correct the effects of media opacity to ensure more consistent and robust risk assessments across all patients.

This study has several strengths, including its dual-cohort design, which combines the rigor of a longitudinal analysis with the generalizability of a large population-based study. However, it has certain limitations that must be acknowledged. First, the cross-sectional design of the population cohort, which compared different individuals with and without a history of cataract surgery, is an inherent limitation as it is not a direct replication of the within-subject longitudinal design of our hospital cohort. Second, our study did not longitudinally assess for major adverse cardiovascular events (MACE). Consequently, we could not confirm whether higher postoperative Dr.Noon CVD scores represented a more accurate prediction of future cardiovascular events. Therefore, to determine whether the postoperative increase in Dr.Noon CVD score after cataract surgery represents a true clinical benefit or instead leads to false-positive factor, performance and reclassification analyses against the ground-truth CVD outcomes should be conducted. Furthermore, future studies should incorporate AUC/PR-AUC, calibration, and reclassification metrics to evaluate the impact on real-world

clinical decision-making (e.g., high-risk stratification, statin recommendations). Future large-scale longitudinal or prospective cohort studies are also needed to validate the long-term prognostic value of these scoring changes. Third, although we adjusted for confounders, the possibility of unmeasured confounders such as systemic medication changes remains. However, because we examined rapid within-subject changes following discrete surgical interventions, the impact of these potential confounders was likely to be limited. Fourth, by including only eyes with gradable images at all time points, we may have introduced a selection bias, potentially excluding patients with severe media opacities. To characterize this, we compared LOCS III scores between eyes excluded due to image quality failure ($n = 325$) and the final included sample ($n = 248$ eyes). Excluded eyes demonstrated significantly higher opacity grades across all LOCS III components (cortical: 2.55 ± 1.78 vs. 1.30 ± 1.30 ; nuclear: 3.85 ± 1.24 vs. 2.80 ± 0.77 ; posterior subcapsular: 1.58 ± 1.37 vs. 0.48 ± 0.99 ; all $P < 0.001$), confirming that eyes with denser cataracts were systematically excluded. Because the unmasking effect would plausibly be largest in eyes with the most severe pre-operative opacity, the effect estimates reported in this study likely represent a conservative lower bound of the true magnitude of cataract-induced CVD score attenuation in real-world clinical populations. Fifth, NO was not assessed as part of the LOCS III grading protocol in this study, despite being the component most directly implicated in the yellow-filter effect invoked to explain the mechanistic basis of our findings. The absence of NO grading prevents direct quantification of the association between nuclear chromophore accumulation and the magnitude of AI-derived CVD score change, and future studies should incorporate systematic NO assessment to formally test this mechanistic hypothesis. Also, camera heterogeneity across cohorts represents an unresolved limitation. The HUGH cohort was imaged using the Topcon DRI OCT Triton, while all participants in the SEED cohort were imaged uniformly using the Canon CR-1 Mark-II non-mydriatic retinal camera, ensuring internal consistency within SEED. Nevertheless, neither cohort used the NW400 system on which the Dr.Noon CVD model was originally trained, and domain shift arising from these cross-platform differences may contribute to systematic offsets in absolute CVD score levels that cannot be fully disentangled from the lens effect. We were unable to perform cross-camera calibration in the present study. The directional consistency of the pseudophakia-CVD score association across two independent cohorts using different imaging devices offers partial, though not definitive, reassurance against camera-driven artifact as the primary explanation for our findings.²⁰

In conclusion, this study demonstrates that media opacity from cataracts is associated with significant attenuation of AI-derived cardiovascular risk scores, a finding replicated across longitudinal and population-based cohorts. Whether this attenuation constitutes true underestimation of cardiovascular risk or reflects altered optical properties of the pseudophakic eye influencing model inputs requires future validation against prospective cardiovascular outcomes. Our findings nonetheless underscore the need for clinicians to interpret these scores with caution in the presence of cataracts, and for AI developers to incorporate lens status and image quality metrics into model design and output interpretation.

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Declaration of Competing Interest

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Appendix A. Supporting information

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