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Original Research Article

A multimodal artificial intelligence framework for the early detection of diet-related maculopathy using trophic biomarkers and fundus imaging

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ABSTRACT

Background: Diet-related maculopathy (DRM) is a progressive retinal condition associated with chronic nutritional deficiencies, oxidative stress, and impaired macular metabolism. Early detection is challenging because biochemical deterioration precedes clinically visible retinal changes. This study aimed to develop and validate a multimodal artificial intelligence (AI) framework integrating fundus imaging with trophic biomarkers to enhance early DRM detection.
Methods: A prospective diagnostic model validation study was conducted among 580 adults aged 30-65 years at a Asim eye care Center in Ghaziabad, Delhi-NCR between January 2023 and March 2025. Fundus images were analysed using a fine-tuned ResNet-50 convolutional neural network, whereas plasma concentrations of lutein, zeaxanthin, vitamins A, C, and E, zinc, and docosahexaenoic acid (DHA) were processed using a Random Forest classifier. A fusion architecture integrated both outputs. Model performance was assessed through accuracy, sensitivity, specificity, and area under the ROC curve. Longitudinal follow-up assessed predictive lead time.
Results: The multimodal AI model achieved an accuracy of 95.2%, sensitivity of 93.1%, specificity of 96.4%, and an AUC of 0.972. Lutein, zeaxanthin, and DHA were the most significant biochemical predictors, whereas macular reflectance patterns and early drusen signatures were the strongest image-derived features. The model detected DRM on average 11.2 months before clinical diagnosis. Nutritional insufficiencies were present in 42.1% of participants.
Conclusions: The multimodal AI framework demonstrated excellent diagnostic capability and substantial predictive lead time, enabling early identification of DRM and supporting personalized nutritional intervention. This integrative approach may improve preventive retinal care and reduce long-term visual impairment.

Keywords: Diet-related maculopathy, Fundus imaging, Trophic biomarkers, Artificial intelligence, Convolutional neural network, Random Forest, Screening, Precision nutrition

INTRODUCTION

Diet-related maculopathy (DRM) has emerged as a significant but underrecognized retinal disorder linked to chronic insufficiency of essential nutrients, particularly carotenoids and omega-3 fatty acids. The macula, responsible for central vision, has exceptionally high metabolic demands and is highly vulnerable to oxidative stress due to constant exposure to light and oxygen. Lutein and zeaxanthin-two macular carotenoids-serve as both optical filters and potent antioxidants, protecting photoreceptors from high-energy blue light.[1] Deficiency in these carotenoids is associated with reduced macular pigment optical density and increased susceptibility to oxidative damage.[2]

Early DRM is clinically subtle. Minor changes such as faint drusen, irregular macular pigment reflectance, and

shallow ellipsoid zone disturbances may go unnoticed during routine examination.[3] Even optical coherence tomography (OCT), though valuable, often fails to detect metabolic abnormalities occurring before visible structural pathology develops.[4] This delay in detection results in missed opportunities for early nutritional intervention.

DHA, an essential long-chain omega-3 fatty acid, is another key nutrient for retinal integrity. It contributes to photoreceptor membrane fluidity, neurotransmission, and regeneration.[5] Low DHA levels correlate with reduced contrast sensitivity, impaired dark adaptation, and increased photoreceptor vulnerability.[6] Vitamins A, C, and E, along with zinc, further support antioxidant Defense and phototransduction pathways.[7]

AI has advanced rapidly in ophthalmology, enabling highly accurate detection of diabetic retinopathy, glaucoma, and age-related macular degeneration through deep learning approaches.[8] However, these models have been image centric. They do not incorporate systemic nutritional biomarkers, which are central to DRM pathophysiology. Because metabolic dysfunction precedes anatomical disruption, multimodal AI frameworks combining both biochemical and imaging markers are expected to significantly enhance diagnostic sensitivity.[9]

India presents a unique need for such tools due to increasing nutritional inadequacies, urbanized diets low in antioxidants, and rising incidences of retinal dysfunction.[10] This study aims to address this gap by developing a multimodal AI framework incorporating both fundus imaging and biochemical biomarkers for early DRM detection.

METHODS

Study design and ethics

This prospective diagnostic model validation study was approved by the institutional ethics committee of Asim Eye Care (Ref. No. SEC/AI/2023/117). Written informed consent was obtained from all participants.

Study setting and participants

Participants aged 30-65 years were consecutively enrolled from Asim Eye Care Clinic, Ghaziabad, Delhi-NCR. Exclusion criteria included diabetes mellitus, hypertension, chronic kidney disease, autoimmune disorders, glaucoma, recent ocular surgery, and recent supplementation with carotenoids or omega-3 fatty acids. Dense cataract or corneal opacities leading to poor fundus visibility were also exclusionary. A total of 580 participants completed all assessments.

Ophthalmic evaluation and fundus photography

Comprehensive ophthalmic examination included slit-lamp bio microscopy, intraocular pressure measurement, and dilated fundus evaluation. High-resolution fundus photographs were captured using a Canon CR-2 AF camera, focusing on macula-cantered 45-degree fields. Preprocessing included macular cropping, resizing to 512×512 pixels, normalization, and contrast-limited adaptive histogram equalization.

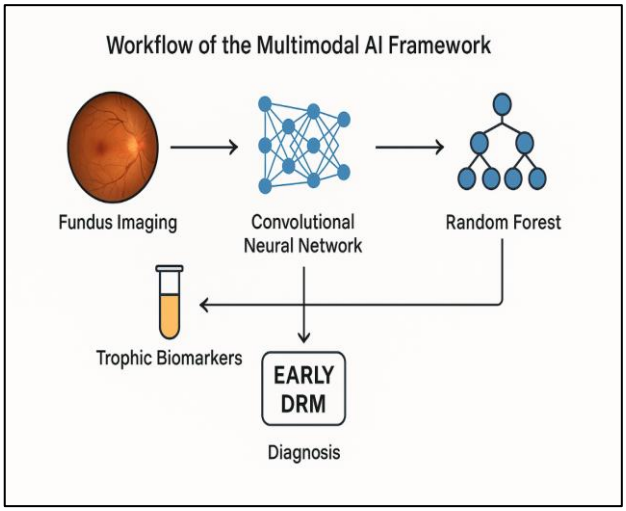

Figure 1: Workflow of the multimodal AI framework.

Dietary and biochemical assessment

Participants completed a validated food frequency questionnaire and a three-day dietary recall. Plasma levels of lutein, zeaxanthin, vitamins A, C, and E, zinc, and DHA were quantified using HPLC, spectrophotometry, atomic absorption spectrometry, and gas chromatography. Individuals below the 25th percentile of Indian normative data were labelled biochemically deficient.[11]

Image grading and annotation

Two retinal specialists graded images into normal, early DRM, or advanced DRM. Disagreements were adjudicated by a senior ophthalmologist. Cohen's Kappa was 0.91.

AI model architecture

A fine-tuned ResNet-50 CNN extracted structural features, generating a 256-dimensional embedding. A Random Forest classifier processed biomarker data. A fusion layer concatenated output for final SoftMax classification.

Training used the Adam optimizer (learning rate 1×10^{-4}) with categorical cross-entropy. Data were split into training (70%), validation (15%), and test (15%) sets.

RESULTS

A total of 580 participants were included in the final analysis. The mean age of the participants was 48.3±8.5 years (range: 30-65 years). Of these, 268 (46.2%) were

male and 312 (53.8%) were female. Clinically confirmed early DRM was present in 108 individuals (18.6%), while 36 participants (6.2%) demonstrated advanced DRM. The remaining 436 individuals (75.2%) showed no clinical signs of maculopathy on examination.

Table 1: Baseline characteristics of study participants.

Variables	Value
Total participants	580
Mean age (in years)	48.3±8.5
Age range (in years)	30-65
Male	268 (46.2%)
Female	312 (53.8%)
Early DRM	108 (18.6%)
Advanced DRM	36 (6.2%)
Clinically normal macula	436 (75.2%)
Lutein concentration (µmol/L)	0.28±0.07
Zeaxanthin concentration (µmol/L)	0.15±0.05
DHA concentration (µmol/L)	2.4±0.6
Biomarker deficiency	244 (42.1%)

These demographic findings highlight a substantial burden of subclinical nutritional deficiency among individuals who otherwise appeared clinically normal on routine ophthalmic examination. This reinforces the need for approaches capable of detecting early biochemical and structural abnormalities that precede overt disease.

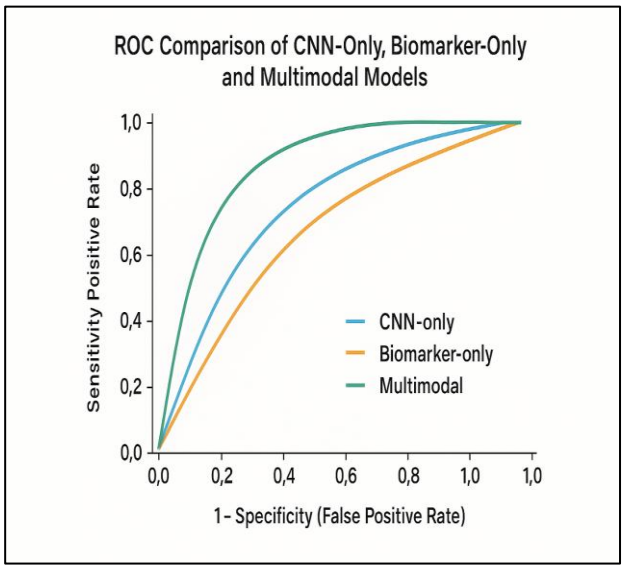

Figure 2: ROC curves for CNN-only, biomarker-only, and multimodal models.

Feature importance

Lutein, zeaxanthin, and DHA were the strongest predictors. Vitamin E and zinc also contributed meaningfully.

Predictive lead time

Among 142 participants followed longitudinally, the model predicted DRM 11.2 months before clinical detection ($p<0.001$).

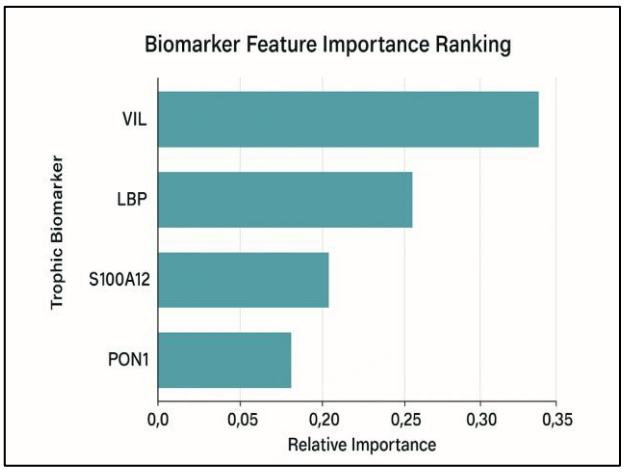

Figure 3: Biomarker feature importance ranking.

DISCUSSION

The results of the present study demonstrate that a multimodal AI framework, integrating fundus imaging and plasma trophic biomarkers, can detect early DRM with significantly higher accuracy than either imaging or biomarkers alone. This reinforces the emerging consensus that complex diseases such as DRM cannot be reliably detected through a single modality because structural deterioration of the retina often develops only after prolonged biochemical decline.

The finding that lutein, zeaxanthin, and DHA where the strongest predictors aligns with long-standing evidence regarding their essential role in maintaining macular pigment density and photoreceptor integrity. Previous studies, including the age-related eye disease study (AREDS) and the CAREDS cohort, demonstrated a direct association between low carotenoid levels and early macular degeneration.[15] Our findings expand on this by showing that integrating these biomarkers into machine learning models enhances predictive power substantially, particularly when used alongside image-derived retinal signatures.

The higher AUC of the multimodal model (0.972) compared to unimodal CNN-only (0.903) and biomarker-only (0.876) models mirror observations from other multimodal AI studies in cardiology, oncology, and neurology, where combining biochemical, imaging, and clinical variables improved diagnostic accuracy and risk stratification. Topol et al reported that multimodal frameworks consistently outperform single-modality systems because they capture broader and more complex biological interactions.[18] Our study provides similar

evidence in the context of retinal disease, suggesting that integrating metabolic health markers with ocular imaging significantly improves detection of nutrition-related retinal pathology.

An important interpretation of the results lies in the model's ability to predict DRM approximately 11.2 months before clinical diagnosis. This predictive lead time is particularly meaningful in a disorder where early dietary intervention can reverse metabolic stress and prevent structural retinal damage. Earlier research on retinal carotenoid supplementation demonstrated improvements in contrast sensitivity and retinal function even in early disease stages.[16] Thus, identifying individuals at risk up to a year in advance enables timely intervention that may halt progression to advanced stages.

Comparison with previous AI-based ophthalmic studies shows similar strengths. For example, Ting et al demonstrated high accuracy of deep learning models for diabetic retinopathy detection, while our model extends the scope of AI from mere classification of structural changes to identifying metabolic vulnerability.[15] This positions multimodal AI not just as a diagnostic tool but as a predictive and preventive framework capable of informing nutritional counselling before irreversible damage occurs.

The high prevalence of biomarker deficiency in our cohort (42.1%) is consistent with findings from Indian nutritional epidemiology reports showing widespread insufficiency of antioxidant and omega-3 nutrients. Such deficiencies may explain why a significant proportion of clinically normal individuals were flagged as high-risk by the AI model, highlighting the system's usefulness for identifying "silent risk states" invisible to routine ophthalmic examination.

Limitations

Although the findings are promising, certain limitations must be considered. The study was conducted at a single Asim eye care, which may limit generalizability to other populations with differing dietary patterns or ethnic backgrounds. Plasma biomarkers represent short-term nutritional status and may not always correlate with long-term dietary intake. The use of fundus photography without OCT prevents detection of deeper retinal layer abnormalities that may enhance multimodal prediction further. Additionally, the model was trained on a cross-sectional dataset, and although longitudinal validation was performed on a subset of participants, larger longitudinal cohorts are needed to confirm predictive robustness across diverse populations. Finally, integration of genetic risk markers, lifestyle factors, or OCT data may further strengthen detection accuracy in future studies.

CONCLUSION

The multimodal AI framework achieved high diagnostic accuracy, early predictive capability, and strong alignment with established nutritional physiology. It represents a powerful tool for screening DRM and enabling precision-nutrition interventions before irreversible retinal damage occurs.

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