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Estimating biological age from retinal imaging: a scoping review

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ABSTRACT

Background/Aims The emerging concept of retinal age, a biomarker derived from retinal images, holds promise in estimating biological age. The retinal age gap (RAG) represents the difference between retinal age and chronological age, which serves as an indicator of deviations from normal ageing. This scoping review aims to collate studies on retinal age to determine its potential clinical utility and to identify knowledge gaps for future research.

Methods Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist, eligible non-review, human studies were identified, selected and appraised. PubMed, Scopus, SciELO, PsycINFO, Google Scholar, Cochrane, CINAHL, Africa Wide EBSCO, MedRxiv and BioRxiv databases were searched to identify literature pertaining to retinal age, the RAG and their associations. No restrictions were imposed on publication date.

Results Thirteen articles published between 2022 and 2023 were analysed, revealing four models capable of determining biological age from retinal images. Three models, 'Retinal Age', 'EyeAge' and a 'convolutional network-based model', achieved comparable mean absolute errors: 3.55, 3.30 and 3.97, respectively. A fourth model, 'RetiAGE', predicting the probability of being older than 65 years, also demonstrated strong predictive ability with respect to clinical outcomes. In the models identified, a higher predicted RAG demonstrated an association with negative occurrences, notably mortality and cardiovascular health outcomes.

Conclusion This review highlights the potential clinical application of retinal age and RAG, emphasising the need for further research to establish their generalisability for clinical use, particularly in neuropsychiatry. The identified models showcase promising accuracy in estimating biological age, suggesting its viability for evaluating health status.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Retinal age has emerged as a promising ageing biomarker capable of determining biological age from retinal images.

WHAT THIS STUDY ADDS

⇒ This study presents a comprehensive scoping review of current literature concerning retinal age and the retinal age gap (RAG), highlighting the reproducible association between advanced RAG and increased mortality and cardiovascular disease risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings underscore the paucity of knowledge on this topic, advocating for further research in this area to determine the potential clinical use of retinal age as a biomarker.

INTRODUCTION

The number of elderly individuals is rising, leading to an increased burden on healthcare services and society. Ageing changes are heterogenous, with substantial variation in health impacts of ageing across populations, individuals and tissues.[1 2] Thus, biological ageing markers have emerged to better represent the ageing process and predict functional capability.

Retinal age, an imaging-based biomarker, provides an estimate of biological age derived from retinal fundus photographs.[3 4] The rationale for retinal age as a biomarker stems from the retina's shared embryological origin with the central nervous system (CNS)[5] and microvascular structure, which is closely related to that of the brain, heart and kidney.[6 7] Although retinal imaging has largely been used by ophthalmologists for understanding and treatment of ocular disease,[8] predictive retinal ageing extends utility of retinal fundus imaging by applying deep learning (DL).

The introduction of the retinal age gap (RAG), the difference between calculated retinal age and chronological age, provides a valuable metric for assessing normal ageing deviations. Compared with traditional biomarker approaches, criticised for their cost, invasiveness, time-consuming nature and suboptimal accuracy, application of retinal age models provides a cost-effective, non-invasive and readily accessible way of estimating biological age,[9 10] particularly suited to large-scale population studies.

To date, there is no review on the reliability of retinal age as a biomarker. Although several biomarker reviews have included retinal age as one of many biological age estimators, they have not provided a comprehensive summary of the accuracy, practical utilisation or relevance of retinal ageing models. This scoping review seeks to consolidate what is known about retinal age, while identifying gaps for future research.

Specifically, this review aims to answer:

- How extensive is the current literature pertaining to retinal age and RAG?
- How many models exist? How accurate are they?
- Does this biomarker have clinical associations? Does it exhibit clinical utility?
- What are pressing future directions for research?

METHODS

Protocol and registration

A scoping review is suited to expand what is known about retinal age, as it allows synthesis of current literature. A protocol was developed for this purpose and registered on Open Science Forum (available at: https://osf.io/fse75/ DOI 10.17605/OSF.IO/FSE75). The format for this review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) checklist and has made use of the Janna Briggs Institute Manual for Evidence Synthesis.

Eligibility criteria

All published literature, and preprints of primary studies of retinal age in adults were included for analysis. No limitations were imposed for publication language or date.

Search

A literature search of the following electronic databases was conducted from 17 to 19 June 2023: PubMed, Scopus, Cochrane Library, CINAHL, SciELO, Google Scholar, PsycINFO, Africa Wide EBSCO Host, MedRxiv and BioRxiv. A librarian assisted with formulating the search strategy. Initial search terms for the PubMed database included the non-MESH terms, “retinal age” AND “association”, which were further refined to ((retinal age [Text Word]) OR (retinal age gap [Text Word])) AND (((association) OR (link)) OR (biomarker)) and adapted for each database searched. Refer to online supplemental appendix 1 for full search strategy used.

Selection

A two-stage selection process was employed. Articles identified through the search strategy were deduplicated. Two reviewers (MJG, S-MK) independently screened titles and abstracts to ascertain eligibility and relevance, using the predetermined inclusion and exclusion criteria. For publications that met inclusion criteria, these criteria were re-applied to the full-text articles. When discrepancies in reviewers’ ratings were observed, a coordinating investigator (JI) conducted a final review to determine inclusion eligibility. Citations within included articles were scanned to identify additional articles suitable for inclusion. Email updates for Google Scholar were enabled to capture newly published literature between the search date and the writing phase. Subsequent articles found were subjected to the same review process.

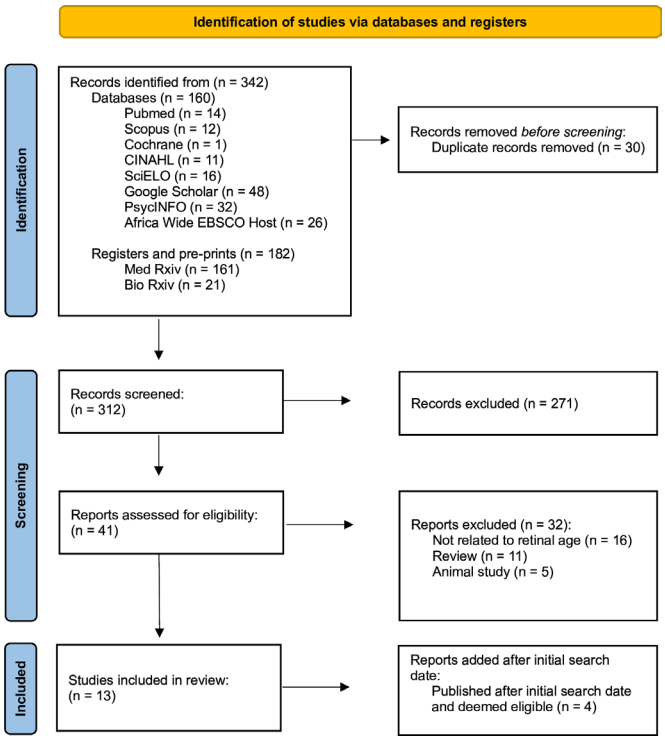

Figure 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram outlines the selection process for studies included in this scoping review.

Data charting process

Data were extracted from the suitable articles using a spreadsheet developed by reviewers. Data extracted included title, publication date, authors, study design, study aims, model type, model development, outcome of interest and key findings.

RESULTS

Selection of sources

The PRISMA flow diagram (figure 1) outlines the selection process. The search strategy yielded 342 articles (online supplemental appendix 1). After application of inclusion criteria, 41 full-text articles were examined for eligibility. Four articles published after the literature search date were considered for inclusion. A total of 13 articles met criteria for inclusion in this review.

Characteristics of the articles

All articles included for review were published between 2022 and 2023. Online supplemental appendix 2 presents a summary of the studies.

Narrative review of study findings

All included studies used DL algorithms for retinal age analysis. Four distinct models capable of determining biological age from fundus photographs are outlined. Their training, validating and testing processes are described below.

Model development and accuracy

Three models can predict age from retinal images, namely: '*Retinal Age*',[4] '*EyeAge*'[11] and '*convolutional network-based model*'.[12] A fourth biological ageing model, '*RetiAGE*',[3] estimates the probability of an individual being older than 65 years.

The '*Retinal Age*' model was trained and validated on 19 200 fundus photographs from 11 052 healthy UK Biobank (UKB) participants, a dataset comprising over 500 000 individuals between the ages of 40 and 69 years at recruitment. The model underwent fivefold cross-validation, achieved a mean absolute error (MAE) of 3.55 and Pearson's correlation coefficient (R) between estimated age and chronological age of 0.80.[4] The '*EyeAge*' model was trained on 217 289 images from 100 692 individuals with a mean age of 54 years in the EyePACS dataset, validated on 54 292 images from 25 238 individuals within the same dataset and tested in both the UKB and EyePACS datasets. The model achieved an MAE of 3.30, and a Pearson's R of 0.87 for the UKB test dataset, with corresponding figures of 2.86 and 0.95 for EyePACS.[11] The '*convolutional network-based model*' was trained on 98 400 photos from patients diagnosed with diabetes, aged 40–90 years, who were enrolled in the Retisalud programme of the Canary Islands Health Service. To validate the model, 1000 images from the dataset were used, achieving a MAE of 3.97. The '*RetiAGE*' model was trained on 116 312 photographs from 36 432 participants of the Korean Health Screening Study with a mean age of 54 years and validated on 12 924 unseen photos from 4048 participants from the same dataset. An internal test on 32 318 photos of 10 171 participants achieved an area under the receiver operating characteristic (AUROC) curve of 0.968 and an area under the precision-recall curve (AUPRC) of 0.83. When applied to the UKB, the model achieved an AUROC of 0.756 and an AUPRC of 0.399 with a correlation of 0.62 between '*RetiAGE*' and chronological age.[3]

Clinical utility and model associations

RAG, previously defined, has conventionally been used as the metric for assessing clinical utility and performance of retinal ageing models in reflecting biological ageing. Eleven papers using two models, '*Retinal Age*' and '*convolutional network-based model*', have been published with RAG as the outcome measure of interest. Table 1 summarises the clinical utility of the four identified retinal ageing models.

Ten association analyses were conducted using '*Retinal Age*' to explore the relationship between RAG and age-related parameters, within the UKB. The introductory study, highlighting the development of the model, revealed a significant association of a 2% increase in mortality risk for each 1-year increase in RAG.[4] Beyond the risk stratification for mortality, several prospective studies have highlighted associations for each 1-year increase in RAG with a 10% increase of Parkinson's disease,[13] a 4% increase of stroke,[14] a 3% increase of incident cardiovascular disease,[15] a 10% increase in risk

Table 1 Clinical utility of retinal ageing models

Model name	Outcome measure	Cohort	Clinical parameters investigated
Retinal Age	RAG	UK Biobank	Increased mortality risk and disease association (Parkinson's disease, stroke, cardiovascular disease, kidney failure, diabetic retinopathy in patients with diabetes) for each 1-year increase in RAG
			Associations between lifestyle diseases (central obesity, higher glycaemia levels, metabolic syndrome)
			Improved cardiovascular health metrics associated with decreased RAG
EyeAge	EyeAge and EyeAge Acceleration (akin to RAG)	EyePACS and UK Biobank	Increased risk of all-cause mortality, COPD, myocardial infarction and elevated systolic blood pressure
			GWAS identified several genes associated with eye function and age-related disorders
Convolutional network-based model	RAG	Patients with diabetes in Retisalud programme	Association with more severe, progressive diabetic retinopathy
RetiAGE	Accelerated ageing	Korean Health Screening Study and UK Biobank	Increased risk of mortality (all-cause, cardiovascular and cancer) for higher quartiles of ageing

COPD, chronic obstructive pulmonary disease; GWAS, genome-wide association study; RAG, retinal age gap.

of incident kidney failure[16] and a 7% increased risk of diabetic retinopathy in patients with diabetes.[17] Several cross-sectional studies using '*Retinal Age*' explored the associations between lifestyle diseases and RAG. Central obesity,[18] higher glycaemia levels[19] and metabolic syndrome[20] were associated with higher RAGs, while a study aimed at correlating RAG with cardiovascular health metrics—comprising 7 metrics with a total score of 14—found that each 1-unit increase in cardiovascular health score was associated with a 13% decrease in calculated RAG.[21]

'*EyeAge*' evaluated its clinical performance by calculating EyeAge Acceleration, determined akin to RAG, as the difference between EyeAge (reflecting retinal age) and chronological age. In the UKB, adjusted '*EyeAge*' achieved an all-cause mortality HR of 1.03, while RAG (referred to as EyeAge Acceleration) was associated with a higher risk of chronic obstructive pulmonary disease, myocardial infarction, elevated systolic blood pressure and fluid intelligence scores. Additionally, a genome-wide association study performed found candidate genes identified for EyeAge acceleration are associated with eye function and age-related disorders.[11]

The '*convolutional network-based model*' determined, from a case-control study in patients with diabetes from the Retisalud programme, that higher RAG was associated with more severe, progressive diabetic retinopathy.[12] Although more severe, progressive diabetic retinopathy cannot simply be equated with ageing, this echoes findings of '*Retinal Age*' in patients with diabetes.[17]

'*RetiAGE*' also used the UKB to assess its clinical performance. In contrast to '*Retinal Age*' and '*convolutional network-based model*', which used RAG for outcome assessment, '*RetiAGE*' directly investigated its association with different age-related outcomes. Individuals placed in higher quartiles of '*RetiAGE*' were considered to have accelerated ageing. Comparing individuals in the fourth quartile group with those in the first quartile, there was a 67% higher risk of 10-year all-cause mortality, a 142% higher risk of cardiovascular-related mortality and a 60% higher risk of cancer-related mortality after adjusting for chronological age and other established ageing biomarkers.[3]

Saliency maps

Features that drive retinal ageing estimates were identified for '*Retinal Age*' and '*RetiAGE*'. '*Retinal Age*' retrieved attention maps using guided Grad-CAM,[22] to highlight pixels in the input retinal fundus image based on their contributions to the final evaluation. Areas around retinal vessels are highlighted, indicating that retinal microvasculature is used by the DL model for age prediction.[4] '*RetiAGE*' generated saliency maps to localise anatomy contributing to retinal ageing. They indicate that '*RetiAGE*' focuses on the macula, optic disc and retinal vessels for age determination.[3]

DISCUSSION

This study aimed to appraise existing research using retinal photography to develop biological ageing markers. We sought to determine the accuracy of retinal age prediction models, evaluate their ability to reflect age-related parameters and explore their clinical associations. This scoping review identified models which estimate chronological age from retinal images with moderate to high accuracy and identified several age-related associations.

Four models are currently available to estimate biological age from retinal images, all based on DL algorithms: '*Retinal Age*',[4] '*EyeAge*',[11] '*convolutional network-based model*'[12] and '*RetiAGE*'.[3] '*Retinal Age*', '*EyeAge*' and '*convolutional network-based model*' were trained to predict numerical chronological age from retinal images, while '*RetiAGE*' was trained to predict the probability of an individual being older than 65 years.

All models were trained and validated using a single dataset, predominantly comprising Caucasian or Asian populations. To enhance robustness, both '*EyeAge*' and '*RetiAGE*' underwent additional internal testing on previously unseen images from the training and validation cohort. For model testing and outcome assessment, the UKB was used by three models: '*Retinal Age*', '*EyeAge*' and '*RetiAGE*'. While the four identified models demonstrated comparable accuracy and performance, it is important to highlight inconsistent reporting of performance metrics, with some pertaining to validation performance, and others test performance. Consequently, the generalisability of these models is uncertain, warranting further work to assess their applicability across diverse populations.

Nevertheless, using retinal age models to predict mortality and morbidity carries significant clinical implications. A key finding from these 13 selected papers emphasises that accelerated ageing, calculated as RAG, age acceleration or other indices, consistently correlates with mortality risk across three models.[3 4 11] In addition, '*Retinal Age*' and '*EyeAge*' show associations with cardiovascular disease, while '*Retinal Age*' and '*convolutional network-based model*' show connections with the risk of diabetic retinopathy in patients with diabetes. These findings highlight the potential of retinal age as an informative tool for quantifying risk of mortality and cardiovascular morbidity. However, no clinical trials have yet explored the utility or feasibility of the models, a crucial aspect for determining their clinical relevance. Furthermore, factors associated with higher RAG, including glycaemic status,[19] central obesity[18] and metabolic syndrome,[20] suggest that RAG may provide valuable insight into lifestyle habits and traits that accelerate ageing.

Reporting of characteristics of populations used for training age prediction models is important. Only '*Retinal Age*' mentions training on healthy populations, a key distinction if one wishes to consider biological age equal to chronological age. The health status of the population used for training '*EyeAge*' and '*RetiAGE*' remains undisclosed, while '*convolutional network-based model*' used

data from patients with diabetes. This may confound the effects of diabetes on apparent ageing, with age itself. Such discrepancies could spark controversy over whether these three retinal age models are accurate predictors of biological age, demanding a standardised procedure for developing biological age.

Additionally, these models were trained on a limited set of retinal features with only two models, '*Retinal Age*' and '*RetiAGE*', producing saliency maps to identify features used for age assessment. This links to concerns about regulatory compliance and interpretability of the use of artificial intelligence in healthcare.[23 24] However, both models alluded to retinal microvasculature being a key component of age ascertainment, indicating that retinal age may reflect ageing related to vascular status. This is supported by the finding that retinal age models are particularly associated with cardiovascular health.[3 21] To improve understanding of retinal features that align with biological age, advanced visualisation techniques are imperative.

The application of retinal age models in predicting neuropsychiatric diseases is relatively underexplored. Given that the retina is an extension of the CNS, it offers a unique and accessible 'window' to visualise cerebral neuronal health.[7] Studies have found that changes in the retina, most notably thinning in the retinal nerve fibre layer, may be associated with certain neuropsychiatric and neurodegenerative diseases.[25] In our review, only one paper using the '*Retinal Age*' model explored RAG in the realm of neuropsychiatry, specifically in the context of Parkinson's disease, leaving this area underexplored.[13] As neurodegeneration is an important aspect of ageing, future studies should concentrate on improving our understanding of the connections between retinal age and neuropsychiatric conditions.

Several limitations of this scoping review deserve emphasis. Publications in non-indexed journals and other 'grey literature' may have been missed. Insufficient data availability precluded quantitative synthesis using meta-analytic statistical techniques. As more literature becomes available, conducting a more extensive review may unveil more diverse associations of retinal age, mechanisms for associations and possibly link retinal age to other biomarkers. Strengths of our study included its development according to a predefined protocol, and application of the PRISMA-ScR.

In conclusion, this scoping review identified four retinal ageing models derived from retinal images, linking advancing RAGs with mortality and cardiovascular disease. It highlights the scarcity of data in the realm of neuropsychiatry, emphasises the need for standardised procedures in developing retinal ageing models and shows that testing across different datasets is crucial to improve the generalisability and utility of the models. Improving our understanding of the biological underpinnings of how these models determine age may too improve their reliability in reflecting ageing processes. Nevertheless, the evidence highlights the potential of retinal age as a biomarker, suggesting its viability as a valuable, cost-effective tool for evaluating health status.

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Supplementary Materials

Appendix 1:

Search of Published Works Databases

Preliminary search strategy formulated on Pubmed.
Initial search terms included: retinal age, retinal age gap, association, link, biomarker.

Database	Date of Search		Search Terms	Results	Articles Screened
Pubmed	17/06/2023	1	(retinal age) OR (retinal age gap)	49 442	14
		2	(retinal age[Text Word] OR (retinal age gap[Text Word])	23	
		3	(retinal age[Text Word] OR (retinal age gap[Text Word]) AND (((association) OR (link) OR (biomarker)	14	
Scopus	17/06/2023	1	Retinal AND age OR retinal AND age AND gap	9 430	12
		2	TITLE-ABS-KEY (“retinal age” OR “retinal age gap”)	29	
		3	TITLE-ABS-KEY (association OR biomarker OR link)) AND TITLE-ABS-KEY (“retinal age” OR “retinal age gap”)	12	
Cochrane	17/06/2023	1	(retinal age OR retinal age gap):ti,ab,kw (Word variations have been searched)	5362	1
		2	(retinal age OR retinal age gap):ti,ab,kw AND (association OR link OR biomarker):ti,ab,kw (Word variations have been searched)	1402	
		3	("retinal age" OR "retinal age gap" OR "retina age"):ti,ab,kw AND (association OR link OR biomarker):ti,ab,kw NOT (age related macular degeneration):ti,ab,kw (Word variations have been searched)	1	
CINAHL	17/06/2023	1	“retinal age” OR “retinal age gap”	3	11
		2	“retinal age” AND “association”	11	
SciELO	17/06/2023	1	Retinal age	223	16
		2	Retinal age gap	0	
		3	Retinal age OR retinal age gap	0	
		4	Retinal age AND association	16	
Google Scholar	18/06/2023	1	“retinal age” OR “retinal age gap” AND association OR link OR biomarker	48	48

PsychINFO	18/06/2023	1	(retinal age OR retinal age gap) AND (association OR link OR biomarker) Boolean/Phrase	32	32
Africa Wide EBSCO Host	18/06/2023	1	(retinal age OR retinal age gap) AND (association OR link OR biomarker) Boolean/Phrase	26	26
Total identified from published databases					160

Search of Preprint Databases

Database	Date of Search		Search Terms	Results	Articles Screened
MedRxiv	19/06/2023	1	“retinal age gap”	161	161
NIH Reporter	19/06/2023	1	“retinal age gap” OR “retinal age” (advanced) Limit to: Project Title, Project Terms, Project Abstract	1 project 4 publications	0
BioArchives	19/06/2023	1	“retinal age”	21	21
Total identified from preprint databases					182

Appendix 2:

Table 1: Cross Sectional Studies – Data Extraction

Article ID	Year	Model Used	Training Dataset	Validating	Testing Dataset	Algorithm Performance	Outcome Measure	Disease of Interest	Associations	Summary
Abreu_2023_Retinal	2023	Based on convolutional networks	Diabetic patients; Retisalud programme of the Canary Islands Health Service; 40-90 years; 98 400 photos	1000 photos	Same as training: 40 - 90 years – 7694 without DR; 5850 with DR (mild - 4505; moderate - 1152; severe - 166; proliferative - 28) = 13544	MAE 3.97	Retinal Age Gap (RAG)	Diabetic Retinopathy (DR)	RAG without DR = 0.609 years; RAG with DR = 1.905 years (p<0.001) -- mild DR 1.541, mod 3.017, severe 3.117, proliferative 8.583; combined mild/no DR = 0.840, mod/severe = 3.131 (p<0.001)	More positive RAG: associated with more progressive DR (p<0.001)
Ahadi_2023_Longitudinal	2023	EyeAge: Deep learning - Inception v3 architecture	EyePACS Dataset; 217 289 images from 100 692 patients; mean age 54.21; 59% female	54 292 from 25 238 patients; mean age 54.2; 58% female	UK Biobank: mean age 56.85 and repeats from EyePACS UKB - 119 952 images from 64 019 patients Mean age 56.85; 55% female	EyePACS MAE 2.86; UKB MAE 3.30	EyeAge; EyeAgeAccel	Age prediction: genetic factors associated with EyeAgeAccel; mortality	EyeAge: All-cause mortality hazard ratio 1.026. EyeAge: morbidity + disability -- EyeAge: COPD (p=0.0048); MI (p=0.049). Increased EyeAgeAccel: increased systolic BP (p=1.025e-7); increased performance in fluid intelligence (p=5.34e-27). GWAS: POC5; GJA3 - eye and age-related functions	EyeAge potential for studying aging; GWAS on 45 555 European individuals - BOLT-LMM v2.3.4 - association found with genetic loci

Chen_2023_Association	2023	Retinal Age: Deep learning - Xception architecture	UK Biobank; 19 200 images from 11 052 healthy participants (40-69 years at recruitment; mean age 52.6 +- 7.97; 53.7% female)	As training - 5-fold validation	UK Biobank: 26 354 included mean age 56.6 +- 8.07; 53.7% female	MAE 3.55; Pearson R 0.80 (p<0.001)	Retinal Age Gap (RAG)	Cardiovascular Health (CVH) - poor (0-7); intermediate (8-10); ideal (11-14)	Each 1 unit score increase in CVH: 13% decrease in RAG (OR=0.87, 95% CI: 0.85-0.90, p<0.001); intermediate/ideal CVH = lower RAG compared to poor CVH (OR=0.76, 95% CI:0.67-0.85, p<0.001; OR=0.58, 95% CI:0.50-0.67, p<0.001); intermediate and ideal CVH=reduced risk of accelerated retinal age compared to poor CVH (OR=0.83, 95%CI:0.77-0.90, p<0.001; OR=0.78, 95%CI:0.71-0.86,p<0.001) ; ideal status of smoking (OR=0.73, 95%CI:0.62-0.87), BMI (OR=0.80, 95%CI:0.71-0.91), BP (OR=0.66, 95% CI: 0.66-0.89) and blood glucose (OR 0.66, 95% CI:0.55-0.80)	Better CVH associated with lower RAG

Chen_2023_Central	2023	Retinal Age: Deep learning - Xception architecture	UK Biobank; 19 200 images from 11 052 healthy participants (40-69 years at recruitment; mean age 52.6 +- 7.97; 53.7% female)	As training - 5-fold validation	UK Biobank 35 550 participants; mean age 56.8 +- 8.04; 55.6% female	MAE 3.55; Pearson R 0.80 (p<0.001)	Retinal Age Gap (RAG)	Central Obesity - WC + BMI: 7 groups	Overweight/high WC, mild obesity/high WC, severe obesity/high WC associated with increased RAG compared to normal weight/normal WC (B=0.333, 95%CI:0.191-0.474, p<0.001; B=0.383, 95% CI:0.257-0.509, p<0.001; B=0.440, 95% CI:0.278-0.602, p<0.001). Overweight/normal WC, mild obesity/normal WC, normal weight/high WC = no significant association with retinal age gaps. Overweight/high WC, mild obesity/high WC, severe obesity/high WC = higher risk of accelerated ageing compared to normal/normal (OR=1.18, 95% CI: 1.08-1.28, p<0.001; OR 1.20, 95% CI: 1.11-1.30, p<0.001, OR 1.27; 95% CI: 1.15-1.41, p<0.001)	Higher RAG associated with central obesity and higher WC

Chen_2023_Glycemic	2022	Retinal Age: Deep learning - Xception architecture	UK Biobank; 19 200 images from 11 052 healthy participants (40-69 years at recruitment; mean age 52.6 +- 7.97; 53.7% female)	As training - 5-fold validation	UK Biobank 28 919 participants (mean 56.8, 55% female)	MAE 3.55; Pearson R 0.80 (p<0.001)	Retinal Age Gap (RAG)	Normoglycaemia (HbA1c <5.7%), prediabetes (HbA1c >5.7 and <6.5%), DM2 (HbA1c >6.5% and/or insulin use) - glucose groups mmol/l (<5.5; 5.5-6.4; 6.5-7.9; 8.0-11.0; >11.1); HbA1c (<5.7%; 5.7-6.1%, 6.1-6.5%, 6.5-6.9%, >6.9%)	Prediabetes and DM2 = higher retinal age gap compared to normoglycemia (B=0.37, 95% CI: 0.24-0.49, p<0.001; B=1.16, 95%CI:0.96-1.35, p<0.001. Each 1 unit increase in HbA1C = higher RAG in all subjects and without DM2 (B=0.37, 95% CI:0.29-0.46, p<0.001; B=0.51, 95%CI: 0.36-0.66, p<0.001). Higher non-fasting plasma glucose associated with higher RAG. Each 1 SD increase of glucose level = significantly associated with increased RAG in all subjects and those without DM2 (B=0.17, 95% CI:0.12-0.22, p<0.001; B=0.23, 95%CI:0.13-0.33, p<0.001). Remained significant after excluding DR.	More positive RAG associated with dysglycemia
Zhu_2023_Association	2023	Deep learning - Xception architecture	UK Biobank; 19 200 images from 11 052 healthy participants (40-69 years at recruitment; mean age 52.6 +- 7.97; 53.7% female)	As training - 5-fold validation	UK Biobank 35 918 participants; mean age 56.6 +- 8.04 years; 55.7% female	MAE 3.55; Pearson R 0.80 (p<0.001)	Retinal Age Gap (RAG)	Metabolic Syndrome (Met S) = >3/5 - abdominal obesity, hypertension, elevated serum HDL, elevated serum triglycerides, hyperglycaemia	Each 1-year increase in RAG: 1% risk increase of MetS (OR = 1.01, 95% CI: 1.00-1.02, p= 0.016). Each 1-year increase in RAG: 1% risk increase in inflammation (OR=1.01, 95% CI:1.00-1.02, p=0.021) and 1% risk increase of MetS and inflammation combined (OR=1.01, 95% CI: 1.00-1.02, p=0.001). Per year increase in RAG: associated with 2% risk increase in abdominal obesity (OR=1.02, 95% CI:1.01-1.02, p<0.001), 1% risk increase in hypertension (OR =1.01, 95% CI:1.00-1.02, p=0.002) and 6% risk	RAG associated with MetS and inflammation

									increase of hyperglycaemia (OR=1.06. 95% CI:1.04-1.07), p<0.001). When compared to participants with RAG in lower quartile, the risk of MetS was significantly increased by 10% in the 3rd quartile and 14% in the 4th quartile (OR=1.10, 95% CI:1.01-1.21, p=0.030, OR=1.14, 95% CI: 1.03-1.26, p=0.012)	

Table 2: Prospective Studies – Data Extraction

Article ID	Year	Model Used	Training Dataset	Validating	Testing Dataset	Algorithm Performance	Outcome Measure	Disease of Interest	Associations	Summary
Chen_2023_Retinal	2023	Retinal Age: Deep learning – Xception Architecture	UK Biobank; 19 200 images from 11 052 healthy participants (40-69 years at recruitment; mean age 52.6 +- 7.97; 53.7% female)	As training - 5-fold validation	UK Biobank 2311 diabetic patients without diabetic retinopathy (DR) at baseline. Mean age 58.5; 39.7% female	MAE 3.55; Pearson R 0.80 (p<0.001)	Retinal Age Gap (RAG)	Incident diabetic retinopathy	Each 1-year increase in RAG: 7% adjusted increase in risk of incident DR [HR=1.07, 95% CI: 1.02-1.12, p=0.004]. RAG in fourth quartile had higher DR risk [HR=2.88, 95% CI: 1.61-5.15, p<0.001]. DR risk increased across RAG quartiles [HR=1.35, 95% CI 1.11-1.64, p=0.002]	More positive RAG associated with increased risk of incident DR

Hu_2022_Retinal	2022	Retinal Age: Deep learning - Xception architecture	UK Biobank; 19 200 images from 11 052 healthy participants (40-69 years at recruitment; mean age 52.6 +- 7.97; 53.7% female)	As training - 5-fold validation	UK Biobank 35 834 participants free of Parkinson's disease (PD) at baseline; 56+-8.04; 55.7% female	MAE 3.55; Pearson R 0.80 (p<0.001)	Retinal Age Gap (RAG)	Incident Parkinson's disease - ICD 9/10 codes - history of PD; incident PD	Each 1-year increase in RAG: 10% increase in risk of PD (HR=1.10, 95% CI: 1.01-1.20, p=0.023). Compared with lowest RAG quartile, the risk of PD was increased in third and fourth quartiles (HR = 2.66, 95% CI: 1.13-6.22, p=0.024; HR = 4.86, 95% CI: 1.59-14.8, p=0.005). Predictive value of retinal age model (AUC = 0.708, 95% CI:0.638-0.778) and risk factor model (AUC=0.717, 95% CI:0.633-0.802) was similar (p=0.821).	More positive RAG associated with future risk of incident PD
Nusinovici_2022_Retinal	2022	RetiAge: Visual Geometry Group (VGG) - deep convolutional neural network architecture	Korean Health Screening Study; 116312 photos from 36 432 participants; mean age 54 +-9.01	12 924 photos from 4 048 participants	56 301 from UK Biobank (mean age 57.1 +- 8.3 years; 46.5% female) used for all-cause mortality, CVD mortality and cancer mortality. 46 551 from Korean Health Screening Study (mean 53.6 +-9.2 years; 45.4% female) used for all-cause mortality.	AUROC 0.968 (95% CI: 0.965-0.970); AUPRC 0.83)95% CI: 0.83-0.84) in internal test AUROC of 0.756 (95% CI: 0.753-0.759) and an AUPRC of 0.399 (95% CI: 0.388-0.410 in UK Biobank test	RetiAge	Predict old age from retina. All-cause mortality; CVD mortality and cancer mortality	Independent of chronological age and phenotypic ageing markers: when compared to RetiAge first quartile, those in the RetiAge fourth quartile had 67% higher risk of 10 year all-cause mortality (HR = 1.67, 95% CI: 1.42-1.95, p <0.001) 142% higher risk of CVD mortality (HR = 2.42, 95% CI: 1.69-3.48, p<0.001) and 60% higher risk of cancer mortality (HR=1.60, 95% CI: 1.31-1.96, p<0.001).	RetiAge can predict aging; higher RetiAge associated with mortality risk

Zhang_2023_Association	2023	Deep learning - Xception architecture	UK Biobank; 19 200 images from 11 052 healthy participants (40-69 years at recruitment; mean age 52.6 +- 7.97; 53.7% female)	As training - 5-fold validation	UK Biobank 35 864 participants with no kidney failure at baseline; mean age 56.75 +- 8.04; 55.7% female	MAE 3.55; Pearson R 0.80 (p<0.001)	Retinal Age Gap (RAG)	Incident kidney failure - ICD 10 and OPCS 4 codes	Each 1-year increase in RAG: 9% increase in risk of incident kidney failure (HR = 1.09, 95% CI: 1.03-1.15, p<0.001). Retinal age gaps in the highest quartile had a significantly higher risk of incident kidney failure compared to those in the first quartile (HR = 2.77, 95% CI: 1.29-5.93, p=0.009). There was a graded association of incident kidney failure across retinal age gap quartiles (p=0.004). Participants in higher RAG quartile showed higher risk of kidney failure event.	More positive RAG associated with incident kidney failure
Zhu_2022_Association	2022	Deep learning - Xception architecture	UK Biobank; 19 200 images from 11 052 healthy participants (40-69 years at recruitment; mean age 52.6 +- 7.97; 53.7% female)	As training - 5-fold validation	UK Biobank 35 541 participants; mean age 56.8 +- 8.04; 55.6% female	MAE 3.55; Pearson R 0.80 (p<0.001)	Retinal Age Gap (RAG)	ASI - arterial stiffness index; CVD events - cardiovascular disease	Each 1-year increase in RAG: increase in ASI (B=0.002, 95% CI: 0.0001-0.003, p=0.001). Higher odd of having severe ASI with a larger RAG (OR=1.01, 95% CI: 1.01-1.02, p<0.001). Each 1-year increase in RAG: predicts 3% increase in risk of incident CVD (HR = 1.03, 95% CI: 1.00-1.05, p=0.019). Remains significant when ASI is incorporated (HR = 1.03, 95% CI: 1.01-1.06, p=0.019)	More positive RAG significantly associated with ASI. RAG predictor of future risk of incident CVD.

Zhu_2022_Retinal	2022	Deep learning - Xception architecture	UK Biobank; 19 200 images from 11 052 healthy participants (40-69 years at recruitment; mean age 52.6 +- 7.97; 53.7% female)	As training - 5-fold validation	UK Biobank 35 304 without stroke history; mean age 56.7 +- 8.04; 55.9% female)	MAE 3.55; Pearson R 0.80 (p<0.001)	Retinal Age Gap (RAG)	Stroke - ICD 9/10 codes	Each 1-year increase in RAG: associated 4% increase in risk of stroke when adjusting for confounding factors (HR=1.04, 95% CI: 1.00-1.08, p=0.029). Retinal age gaps in the 5th quintile had higher risk of stroke compared to those whose RAG was in the first quintile (HR=2.37, 95% CI:1.37-4.10, p=0.002). Predictive capability of retinal age alone in 10-year stroke risk was comparable to a well-established risk factor-based model (AUC=0.676 vs AUC 0.661, p=0.511)	More positive RAG associated with incident stroke
Zhu_2023_Retinal	2023	Deep learning - Xception architecture	UK Biobank; 19 200 images from 11 052 healthy participants (40-69 years at recruitment; mean age 52.6 +- 7.97; 53.7% female)	As training - 5-fold validation	UK Biobank 35 913 photos from 35 917 participants; mean age 56.8 +- 8.04; 55.7% female	MAE 3.55; Pearson R 0.80 (p<0.001)	Retinal Age Gap (RAG)	All-cause mortality	Each 1-year increase in RAG: 2% increase in mortality risk (HR = 1.02, 95% CI 1.00-1.03, p=0.020); Positive retinal age gap: substantially increased mortality; Higher retinal age gap (3rd and 4th quartile): higher non-CVD/cancer associated death (HR=1.49, 95% CI 1.13-1.96, p=0.005; HR=1.67, 95% CI 1.17-2.39, p=0.005)	More positive RAG associated with increased risk of mortality (>non-CVD/non-cancer)

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3-4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	4
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	4
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	4
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	4-5
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	5
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	/
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	5

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	5
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	5, appendix 2
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	/
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	7-9
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	7-9; appendix 2
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	9-11
Limitations	20	Discuss the limitations of the scoping review process.	11
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	11
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	12

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

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