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REVIEW ARTICLE

Should clinical automated perimetry be considered for routine functional assessment of early/intermediate age-related macular degeneration (AMD)? A systematic review of current literature

Matt Trinh[1,2] | **Michael Kalloniatis**[1,2] | **Lisa Nivison-Smith**[1,2]

[1]Centre for Eye Health, University of New South Wales, Sydney, New South Wales, Australia

[2]School of Optometry and Vision Science, University of New South Wales, Sydney, New South Wales, Australia

Correspondence
Lisa Nivison-Smith, Centre for Eye Health, University of New South Wales, Sydney, New South Wales, Australia.
Email: L.nivison-smith@unsw.edu.au

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Abstract

Purpose: There is growing interest in functional testing for early/intermediate age-related macular degeneration (iAMD). However, systematic evaluation of existing clinical functional tests is lacking. This systematic review examines evidence for using clinical automated perimetry in routine assessment of early/iAMD.

Recent findings: PubMed, Web of Science Core Collection, and Embase were searched from inception to October 2020 to answer, is there evidence of visual field defects in early/iAMD, and if so, are early/iAMD visual field defects linked to real-world patient outcomes? Articles using clinical automated perimetry (commercially accessible and non-modified devices/protocols) were included. Microperimetry was excluded as this has yet to be incorporated into clinical guidelines. The primary outcome was global visual field indices including mean deviation (MD), pattern standard deviation (PSD), mean sensitivity (MS) and frequency of defects. The secondary outcome was any real-world patient outcome including quality of life and/or activities of daily living indices. Twenty-six studies were eligible for inclusion and all studies were observational. There was consistent evidence of worsened MD, PSD, MS and frequency of defects for early/iAMD compared to normal eyes under photopic, low-photopic and scotopic conditions. Meta-analysis of studies using standard automated perimetry (SAP) under photopic conditions revealed worsened MD (−1.52dB [−2.27, −0.78 dB]) and MS (−1.47dB [−2, −0.94 dB]) in early/iAMD compared to normal eyes, representing large statistical effect sizes but non-clinically meaningful reductions. There was insufficient data for meta-analyses regarding other clinical automated perimetry protocols. Only one study assessed a real-world patient outcome (on-road driving performance), with no significant link to visual field outcomes in early/iAMD.

Summary: Significant reduction of global visual field indices is present in early/iAMD, but not clinically meaningful using SAP under photopic conditions. Translational relevance of visual field outcomes to patient outcomes in early/iAMD

remains unclear. Thus, SAP under photopic conditions is unlikely to be useful for routine assessment of early/iAMD.

KEYWORDS
age-related macular degeneration, automated perimetry, photopic, visual fields

INTRODUCTION

Age-related macular degeneration (AMD) is one of the leading causes of irreversible blindness for people over 50 years of age.[1] The appropriate management of AMD involves being able to accurately identify and promptly act upon significant disease progression either through increasing the frequency of clinical reviews, counselling for modifiable risk factors and/or medical intervention.

Current clinical testing for AMD progression is based upon structural assessment of outer retinal biomarkers such as drusen, pigmentary abnormalities, atrophy and neovascularization.[2–9] Visual functional changes in AMD also occur and have been detected via a range of measures such as visual acuity, reading speed, contrast sensitivity, temporal function, visual adaptation (including dark adaptation and photostress recovery), perimetry, colour vision and multifocal electroretinography.[10–17] Furthermore, functional biomarkers in early/iAMD have been linked to structural alterations, disease severity and risk of progression,[17,18] and may even precede clinically-detectable structural impairment in AMD.[19] Yet, very few functional tests are routinely performed in the clinic for AMD patients.

Current standardized clinical functional testing of AMD, i.e., visual acuity, contrast sensitivity and the Amsler grid, provide brief and/or imprecise glimpses of patients' visual functional status with little to no spatial discrimination. These measures also do not consider the pathophysiological underpinnings of AMD. For example, visual acuity typically presents information solely about foveal, high-contrast acuity despite the fact that AMD is not exclusively a foveal disease nor do the early stages of AMD confer any significant visual acuity loss.[20] Meanwhile, contrast sensitivity and the Amsler grid demonstrate poor sensitivity and/or repeatability with regards to the detection of functional change in early/iAMD.[18,21]

Static automated perimetry as it is currently used in clinic[22,23] has effectively fortified clinical diagnoses and monitoring of spatial visual function in ocular diseases such as glaucoma and other optic neuropathies.[24] Visual functional impairment also occurs in early/iAMD,[17] alluding to a potential role for routine automated perimetry in these patients. However, there is a lack of synthesis exploring the role of clinical automated perimetry for the assessment of early/iAMD. Recently, there are rising research interests in studying macular disease via microperimetry, which is based upon the same psychophysical principles but mostly under low-photopic/mesopic or scotopic conditions.[25] First, there is need for a quantified, systematic review investigating whether automated perimetry in its current clinical form may yield clinically meaningful data in early/iAMD.

Key points

- Significant statistical reduction of global visual field indices is present but not clinically meaningful for routine, standard lighting (photopic) functional assessment of early/intermediate age-related macular degeneration.
- There is a distinct lack of studies translating visual field indices to real-world patient outcomes in early/intermediate age-related macular degeneration.
- Further studies examining visual field indices under non-standard (mesopic and scotopic) lighting conditions are required to determine suitability of visual fields for routine assessment of early/intermediate age-related macular degeneration.

The key recommendation for inclusion of a clinical test is proof that the test improves patient outcomes.[26-28] Hence, to investigate whether automated perimetry in its current clinical form should be part of routine functional assessment of early/iAMD, we asked, is there evidence of visual field defects in early/iAMD, and if so, are early/iAMD visual field defects linked to real-world patient outcomes?

METHODS

This systematic review adhered to the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[29] and Rudnicka *et al*.[30]

Literature search strategy

Literature searches were developed *a priori* and performed using the electronic databases PubMed, Web of Science Core Collection and Embase (OVID), for all published journal articles from inception to 12 October 2020. This combination of databases guaranteed adequate and efficient coverage of the literature.[31] Searches were limited to

publications in English using the search terms described in Supplementary *Table S1*. Where available, relevant indexed terms were selected and exploded. As Web of Science did not have relevant indexed terms, keywords were searched instead. All subheadings were included to ensure comprehensive search results. Searches through Imaging and Perimetry Society articles were also performed. Conference abstracts were not included due to their limited data. Searches through reference lists of selected studies and relevant review studies were also performed, although review studies themselves were not eligible for inclusion.

Definition of clinical automated perimetry

In this review, clinical automated perimetry was defined as a group of current clinical, systematised testing devices that measure differential light sensitivities of the visual system to stimuli of varying luminance at pre-determined spaces in the visual field.[32] The 'clinical' prefix as used in this review refers to commercially accessible, non-modified automated perimetry devices and protocols for hardware and software that may be used in current ocular healthcare settings, as mentioned in two key clinical guidelines: the European Glaucoma Society Terminology and Guidelines for Glaucoma,[22] and the Assessment of Visual Function in Glaucoma by the American Academy of Ophthalmology.[23] These included standard (white-on-white) automated perimetry, flicker perimetry and frequency-doubling technology, each of which is defined below. Different lighting conditions were included in this review if part of commercially accessible and non-modified automated perimetry devices and protocols for hardware and software. Specifically, background luminance of 10 cd/m^2 was considered photopic, 3.2 cd/m^2 was considered low-photopic,[33,34] and 0 cd/m^2 was considered scotopic. Studies that did not specify lighting conditions were presumed to operate at the device/protocol's default settings. Short-wavelength automated perimetry (SWAP) was excluded as its clinical use is actively recommended against in the more recent guideline, due to no evidence of 'better performance' compared to other visual field protocols.[22] Discontinued automated perimetry such as high-pass resolution perimetry or the Friedmann Visual Field Analyser were excluded. Microperimetry (also known as fundus perimetry or SLO-guided perimetry) was excluded as this has not yet been incorporated into clinical guidelines.[22,23]

Standard automated perimetry (SAP; white-on-white protocol)

White-on-white SAP is currently the clinical gold standard in automated perimetry, quantifying observers' perception of static, varying contrasted achromatic stimuli (typically Goldmann size III, GIII) on a white background of constant luminance, primarily under photopic conditions.[23,35,36]

Current SAP devices include the Humphrey Field Analyser (Carl Zeiss Meditec, zeiss.com), Medmont automated perimeter (Medmont, medmont.com.au), Octopus static automated perimeter (Haag Streit, haag-streit.com) and the Henson perimeter (Topcon, topconhealthcare.com).

Flicker perimetry

Flicker perimetry is a variant protocol of SAP, presenting flickering stimuli instead of static stimuli. The relatively large, motion-based stimuli of flicker perimetry were originally thought to selectively target the magnocellular sub-cortical visual pathway,[37,38] which may be more susceptible to impairment due to the lesser population of corresponding retinal neurons.[39,40] However, stimulation of the magnocellular pathway has also been observed in SAP.[41] Therefore, differences between flicker perimetry and SAP output cannot be due exclusively to stimuli motion, and may instead be due to varying stimulus size and contrast range.[41-43]

Current flicker perimetry devices include the Medmont automated perimeter (Medmont, medmont.com.au) and the Octopus static automated perimeter (Haag Streit, haag-streit.com). 'Flicker protocols' vary depending on the manufacturered device. The Medmont automated perimeter measures contrast thresholds for a set of temporal frequencies, also known as contrast modulation perimetry (note that temporal frequency varies with eccentricity when using the 'autoflicker' protocol). The Octopus measures the maximum flicker rate at which the observer can distinguish flicker from a uniform state, i.e., the critical flicker frequency threshold.[39] There is limited evidence comparing the performance of 'flicker protocols' in relation to each other, and in comparison to SAP.[44-49]

Frequency-doubling technology (FDT)

Frequency-doubling technology is an alternate, discrete modality of automated perimetry that presents relatively large, achromatic, 'pseudo-flicker' stimuli. The illusion of doubled-frequency flickering stimuli is created from high temporal frequency counterphase modulation of low spatial frequency sinusoidal gratings. The perceptual mechanisms behind FDT are similar to flicker perimetry.[39,40,41,50,51] Studies of FDT compared to SAP have revealed some comparability in results.[52–60]

Current FDT devices include the first-generation Humphrey FDT (Welch Allyn, welchallyn.com) and the second-generation Humphrey Matrix (Carl Zeiss Meditec, zeiss.com).

Selection of studies

Inclusion criteria for this review were studies that used clinical automated perimetry as defined above, for the study of treatment-naïve, early and/or iAMD eyes.[61] Studies which used alternate classifications of AMD such as 'age-related maculopathy' were included if the majority (>50%) of their AMD group were commensurate with the Beckman Initiative classification of early and/or iAMD.[61] AMD groups that included eyes with any late AMD signs such as neovascularisation and/or geographic atrophy were excluded. There were no restrictions with regards to demographic characteristics of the study groups. Studies that used participants with AMD under 55 years of age[61] were still included (as has been done in other notable studies),[62–65] provided that all AMD phenotypic criteria in the Beckman Initiative classification were met.

Exclusion criteria were studies that used non-clinical automated perimetry. Automated perimetry, which was limited to screening/suprathreshold testing protocols, were also excluded. Studies without any relevant comparative group (such as control, baseline, AMD severity or phenotype) were excluded.

Initial search results were exported via Comma Separated Values files into Microsoft Excel version 2107 (Microsoft, microsoft.com) and assessed by two authors (MT and LNS) independently. Duplicate studies between database search results were manually removed and remaining studies were screened by title, abstract and then full text. Eligible studies were then compared between MT and LNS, with disagreements resolved by discussion and consensus.

Quality assessment

Quality assessment of included studies was performed by MT and LNS, and adapted from the Users' Guides to the Medical Literature.[28,66] These tools were selected based on their seminal articulation of evidence-based medicine[67] and informative approach towards the critical appraisal of studies against other quality assessment tools.[68] Criteria used for quality assessment is shown in Supplementary *Table S2*. Data extracted for quality assessment and description of study characteristics included:

- authors, publication year and study type (indicative of patient selection method);
- study location and funding and conflict of interest statements;
- AMD classification scheme used and sample sizes (and whether age was controlled or adjusted for between groups, indicative of comparability of study groups);
- testing conditions such as testing protocol/device, radius/area, threshold strategy, stimulus size and background luminance;
- relevant outcomes to this review (with reported statistical significance; and whether longitudinal and/or dose-response relationships were analysed).

Risk of bias

Risk of bias assessment was performed by MT and LNS, and graded as high, low or unclear risk according to the domains: (1) patient selection and (2) comparability of study groups. Sponsorship bias (i.e., funding and conflict of interest statements) was not added to the risk of bias assessment as it is not officially recognised as a risk of bias domain.[69,70]

These domains were adapted from the QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies[71] and the Newcastle-Ottawa Scale for Assessing the Quality of Nonrandomised Studies in Meta-analyses[72] to guide risk of bias assessment among observational studies. Criteria used for risk of bias assessment are shown in Supplementary *Table S3*. High risk of bias in each domain was defined as a 'no' in any signalling question. Low risk of bias in each domain was defined as a 'yes' in all signalling questions. Unclear risk of bias in each domain was defined when there was insufficient study data to determine a clear 'yes' or 'no' to any signalling question.

Outcomes

The primary outcome was global visual field indices including mean deviation (MD), pattern standard deviation (PSD), mean sensitivity (MS) and frequency of defects in early and/or iAMD eyes compared to normal eyes. Global visual field indices were reported separately for identical lighting conditions where available. Specifically, MD describes average deviation from age-corrected reference sensitivities, PSD describes departure from the normal hill-of-vision based on MD and age-corrected reference sensitivities and MS describes average sensitivity. Definitions were based on the Imaging and Perimetry Society Guidelines with respect to the Humphrey Field Analyser formulae due to the device's extensive usage in the literature for this review.[32] Similar global visual field indices to the above with alternate terminology, but equivalent definitions, were combined for analysis. Similar global visual field indices to the above with non-equivalent definitions, e.g., mean defect, pattern defect, local spatial variation, etc., were reported individually and definitions may be seen in the respective studies and/or the Imaging and Perimetry Society Guidelines,[32] with comparisons observed elsewhere.[73]

Where available, visual field outcomes were also explored in relation to a dose-response gradient (if there were global visual field indices change with increasing AMD severity), and longitudinally. Significant outcomes in the context of a dose-response and longitudinal relationship are thought to enhance confidence in a putative cause-effect relationship.[74,75] The secondary outcome was

any real-world patient outcome including quality of life and/or activities of daily living indices, related to the primary outcome.

Studies which had relevant outcome(s), regardless of whether it was part of the study's primary outcome or not, were included, e.g., data from treatment-naïve (placebo) early/iAMD eyes from randomised controlled trials were included if relevant. All relevant outcomes in the published study were reported, if available, with no additional contact to the study authors. Unclear outcomes, e.g., unclear statistical significance, were reported as such, while missing outcomes were considered unavailable.

Statistical analysis

Statistical meta-analyses were performed using the Review Manager (RevMan) computer program version 5.4.1 (The Cochrane Collaboration, revman.cochrane.org). Meta-analysis was performed only where more than two studies with related data were available to ensure meaningful results. Meta-analyses were grouped by testing protocol, i.e., SAP, flicker perimetry, or FDT, and by identical lighting conditions to maintain validity in comparing results. Study groups that did not control or adjust for ages between groups were excluded from meta-analyses. In studies where more than one relevant effect size was available, e.g., control group data being compared twice to separate early and iAMD classification group data, the latter groups were pooled particularly to reduce bias associated with duplicate study effects.[76,77] For calculation of pooled effect sizes, study weighting was assigned according to the inverse standard error, and random effects models were used to provide more conservative estimates particularly among significant study heterogeneity.[78] Pooled effect sizes were described based on Cohen *et al*.,[79] i.e., 0.2 = small, 0.5 = medium, 0.8 = large. Data were represented as standard forest plots. Inter-study heterogeneity were assessed using Tau^2, Chi^2 and I^2 whereby I^2 from 0%–40% may not be important, 30%–60% may represent moderate heterogeneity, 50%–90% may represent substantial heterogeneity and 75%–100% may represent considerable heterogeneity.[80,81] In cases where meta-analysis resulted in $I^2 \geq 50\%$, the individual study results were investigated. In cases where meta-analysis was not possible, the individual study results were investigated. Default statistical significance was considered as $p < 0.05$.

RESULTS

Selection of studies

The electronic database searches yielded 2223 studies and 1740 unique studies, with 1683 studies excluded after being screened by title/abstract and 33 studies excluded after being assessed by full text (*Figure 1*). The primary reasons for exclusion by full text are provided in Supplementary *Table S5*. No additional studies were identified through the Imaging and Perimetry Society articles. Two additional studies were identified through reference lists of selected studies or relevant review studies. Thus, a total of 26 unique studies were eligible for inclusion. The number of eligible studies per search query are provided in Supplementary *Table S1*. Reviewers MT and LNS were in agreement for all included and excluded studies, with three of the 26 final included studies requiring brief discussion and resolution as relevant data were not immediately obvious.

Quality assessment and study characteristics

Quality assessment details and study characteristics for the 26 included studies can be seen in Supplementary *Table S4*. All studies were observational studies, with the majority being case-control studies (n = 19/26),[15,49,82–98] followed by cohort studies (n = 5/26),[48,99–102] and cross-sectional studies (comparison between groups that did not involve a control or baseline group, but instead defined groups by AMD severity or phenotype; (n = 2/26).[103,104] Feher *et al*.[102] had their study type re-classified from a randomised controlled trial to a cohort design, as for the purposes of this review, only longitudinal data from the treatment-naïve (placebo) early/iAMD eyes were extracted.

Studies were conducted in Australia (n = 11/26),[15,48,49,83,84,87–89,97,100,101] USA (n = 6/26),[85,94,95,98,99,103] Italy, (n = 3/26),[92,93,96] China,[86] Hungary,[102] India,[104] Korea,[91] Sweden[90] and the UK[82] (n = 1/26 for each remaining country). The majority of studies included funding source(s) (n = 19/26)[15,48,49,82,84,85,87,88,90,92–95,97–100,103,104] and conflict of interest statements (n = 15/26),[15,48,49,82,85,88,91,93,94,95,97–100,104] provided in Supplementary *Table S6*. Four studies[48,49,88,100] had funding or conflict of interest associated with clinical automated perimetry.

Over one-third of included studies used an uncommon or outdated classification scheme for AMD such as 'age-related maculopathy' (n = 9/26),[83,84,86,87,90–93,103] which was expected as all but one[91] of these studies were published prior to the Beckman Initiative classification.[61] The remainder used the Age-Related Eye Disease Study classification[105] (AREDS; n = 9/26)[85,89,94–97,99,101,104]; the International Classification and Grading System[106] (ICGS; n = 5/26)[15,48,49,100,102]; the Beckman Initiative classification[61] (n = 2/26)[88,98] and the Rotterdam study classification[107] (n = 1/26).[82] Study sample sizes varied from four to 827 eyes with early and/or iAMD and four to 1007 normal eyes. Age as a significant co-variable affecting global visual field indices were controlled or adjusted for in 23/26 studies.[15,48,49,82–85,87,88–101,103]

Testing conditions, i.e., visual field testing device/protocol, radius, threshold strategy, stimulus size, background luminance, etc. also varied across all studies. The most commonly used testing device was the Humphrey Field Analyser (n = 19/26),[82,84,85,87–95,97,98,99,101–104]

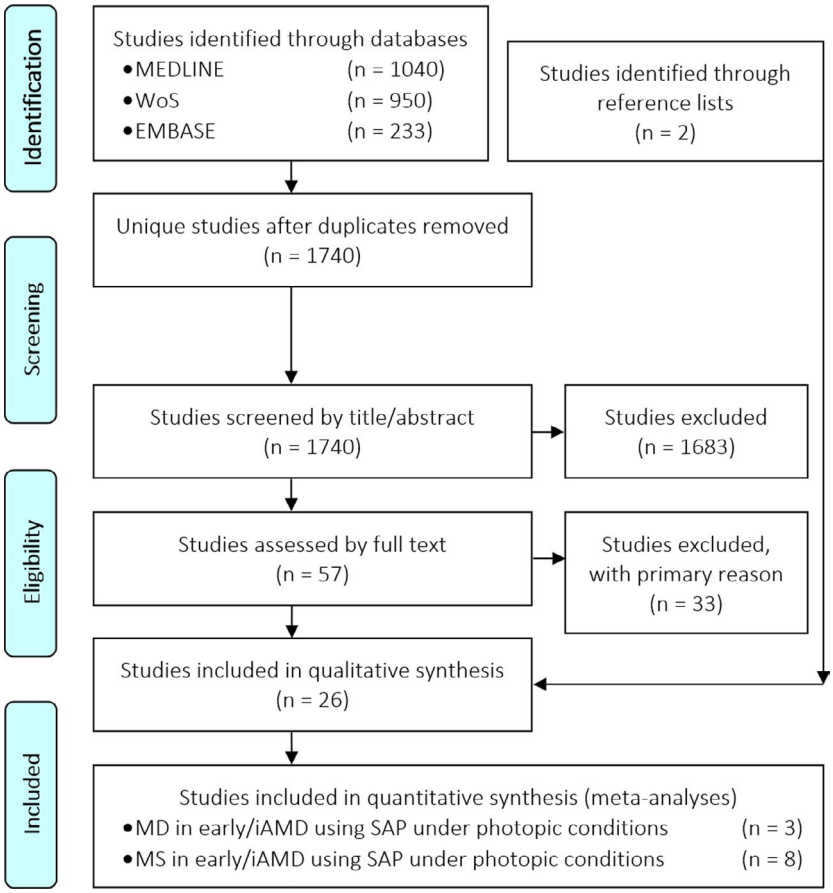

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram[29] for the selection of studies. iAMD, intermediate age-related macular degeneration; MD, mean deviation; MS, mean sensitivity; SAP, standard automated perimetry; WoS, Web of Science Core Collection

followed by the Medmont automated perimeter (n = 5/26),[15,48,49,83,100] the Octopus static automated perimeter (n = 2/26)[86,96] and the first-generation Humphrey FDT (n = 1/26).[83] Testing protocols included: SAP under photopic conditions (10 cd/m^2; n = 21/26)[49,82,84–99,101–104]; SAP under low-photopic conditions (3.2 cd/m^2; n = 3/26)[48,49,83]; SAP under scotopic conditions (0 cd/m^2; n = 1/26)[86]; flicker perimetry under low-photopic conditions (3.2 cd/m^2; n = 5/26)[15,48,49,83,100] and FDT under photopic conditions (100 cd/m^{2108}; n = 1/26).[83] Some studies used more than one test device/protocol. Additional testing conditions were included if mentioned: inclusion of practice exam; prior perimetry experience; pupil status; background lighting adaptation; spatial area analysed (if different to the testing radius); study groups (if sub-divided beyond early and/or iAMD and normal eyes) and follow-up time. Further details of testing conditions are seen in Supplementary *Table S4*.

All studies measured outcomes in the same way between the groups being compared. In the five cohort studies,[48,99–102] follow-up times ranged from one to three years and was not sufficiently long considering the protracted natural history of AMD.[109] Eight studies[48,82,87,92,93,97,103,104] explored a potential dose-response gradient.

Risk of bias

Risk of bias assessment for the 26 included studies can be seen in Supplementary *Table S7*. Regarding patient selection, almost all studies (n = 25/26)[15,48,49,82–101,103,104] had a high risk of bias while one study[102] had a low risk of bias. Regarding comparability of study groups, few studies (n = 4/26)[86,94,102,104] had a high risk of bias while most studies (n = 22/26)[15,48,49,82–85,87–93,95–101,103] had a low risk of bias. No studies had unclear risk of bias. All studies had at least one domain with a high risk of bias.

Primary outcome – global visual field indices

Decreased mean deviation (MD) in early/intermediate age-related macular degeneration (iAMD) versus normal eyes

Photopic conditions

Three studies [#ID 1, 13, 26][82,91,97] reported MD of early/iAMD eyes in comparison to normal eyes using SAP under photopic conditions (Supplementary *Table S4*).

These studies all controlled or adjusted for age between groups. The studies however used different sample sizes (20–76 early/iAMD eyes and 22–100 normal eyes), different classifications of early/iAMD and different testing conditions, potentially contributing to heterogeneous outcomes.

Data from the three studies [#ID 1, 13, 26][82,91,97] were collated for meta-analysis, including assessment of heterogeneity to determine if the above study design differences may have significantly varied the study results (*Figure 2*). The combined sample size was 162 early/iAMD eyes and 198 normal eyes. The total MD mean difference between early/iAMD and normal eyes was −1.52dB [95% CI −2.27, −0.78 dB], i.e., worsened, with a large and significant effect size (Z = 4, $p < 0.0001$). The estimates may have represented moderate-to-substantial heterogeneity not reaching statistical significance (I^2 = 60%, Chi^2 $p = 0.08$). As I^2 was ≥50%, individual study results were further investigated. There were two notable differences between the three studies [#ID 1, 13, 26].[82,91,97] First, different classifications of early/iAMD were used including the Rotterdam study,[107] 'dry AMD',[91] and AREDS classifications respectively, with a further sub-group defined as the 'better eye' and 'worse eye' in Wood *et al*.[#ID 26].[97] Second, each study also used varying visual field testing protocols including radii of 10°, 30° and 24–2, respectively. These differences likely contributed to the moderate-to-substantial heterogeneity of meta-analysis results, although all three studies commonly reported statistically significant decreased MD in early/iAMD (ranging from −0.8dB [−1.6, 0 dB] to −2.23dB [−3.37, −1.09 dB]).

Low-photopic conditions

Phipps *et al*. [#ID 22][49] reported a similar index 'mean defect' mean difference using SAP (Medmont automated perimeter, 10° radius) and flicker perimetry (10° radius) under low-photopic conditions. Twenty-five AMD eyes (modified ICGS classification)[106] were compared to 34 normal eyes with age accounted for. Mean defect was increased (worsened) in AMD eyes using both SAP (mean ± SD, 1.8 ± 0.6 dB) and flicker perimetry (4.3 ± 0.6 dB). No studies explored MD (or equivalent) under scotopic conditions.

Increased pattern standard deviation (PSD) in early/intermediate age-related macular degeneration (iAMD) versus normal eyes

Photopic conditions

Two studies [#ID 1, 13][82,91] reported PSD of early/iAMD eyes in comparison to normal eyes using SAP under photopic conditions (Supplementary *Table S4*). These studies had differing sample sizes (20 and 76 early/iAMD eyes, 22 and 76 normal eyes, respectively) and both controlled or adjusted for age between groups. Classification of early/iAMD used the Rotterdam study[107] and 'dry AMD'[91] classifications, respectively. Both studies also used differing testing radii of 10° and 30°, respectively. These differences likely contributed to the dissimilar results, whereby Acton *et al*. [#ID 1][82] showed no significant difference and Lee *et al*. [#ID 13][91] showed significantly increased (worsened) PSD (2.38dB [2.16, 2.6 dB]) in their respective comparisons of early/iAMD to normal eyes.

Low-photopic conditions

Phipps *et al*. [#ID 22][49] reported a similar index 'pattern defect' mean difference using SAP (Medmont automated perimeter, 10° radius) and flicker perimetry (10° radius) under low-photopic conditions. Comparing 25 AMD eyes (modified ICGS classification)[106] to 34 normal eyes with age accounted for, resulted in increased (worsened) pattern defect using both SAP (5.2 ± 0.4 dB) and flicker perimetry (7.6 ± 0.5) excluding non-zero values. No studies explored PSD (or equivalent) under scotopic conditions.

Decreased mean sensitivity (MS) in early/intermediate age-related macular degeneration (iAMD) versus normal eyes

Photopic conditions

Fourteen studies [#ID 1, 2, 5–7, 9–11, 13, 16–19, 24][82,84,86–95,98,101] reported MS of early/iAMD eyes in comparison to normal eyes using SAP under photopic conditions (Supplementary *Table S4*). Varying sample sizes (11–253 early/iAMD eyes and 8–1007 normal eyes), classifications of early/iAMD, and different testing conditions potentially contributed to heterogeneous outcomes. Chen

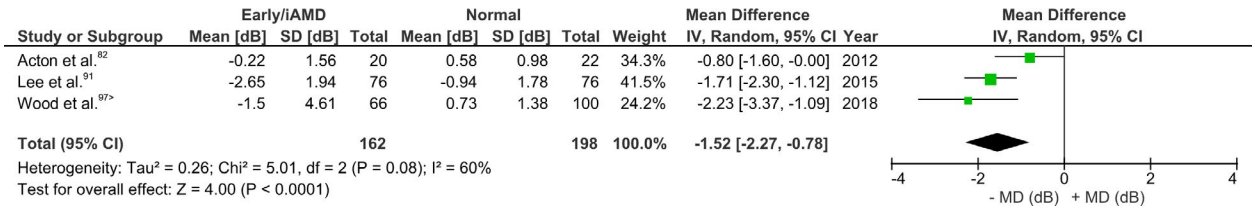

FIGURE 2 Forest plot of mean deviation (MD) mean differences between early/intermediate age-related macular degeneration (iAMD) and normal eyes using standard automated perimetry (SAP) under photopic conditions. Negative values indicate worsened mean deviation (MD) in early/intermediate age-related macular degeneration (iAMD) versus normal eyes

et al. [#ID 5][86] did not control or adjust for age between groups and was subsequently excluded from meta-analysis. Neely *et al*. [#ID 18][94] was also excluded from meta-analysis, as although age was adjusted for between eyes with subretinal drusenoid deposits (SDDs) versus without SDDs, age was not controlled or adjusted for between AMD and normal eyes. Owsley *et al*. [#ID 19][95] was excluded from meta-analysis as their control group was AREDS stage 1 eyes, which overlaps with AMD classification in other studies. A further three studies [#ID 2, 7, 11][84,88,90] were excluded from meta-analysis as data were not available to calculate MS mean differences between early/iAMD and normal eyes.

The eight remaining studies [#ID 1, 6, 9, 10, 13, 16, 17, 24][82,87,89,91–93,98,101] were collated for meta-analysis including assessment of heterogeneity (*Figure 3*). The iAMD (but not early AMD) group from Sevilla *et al*. [#ID 24][98] were older than comparative groups and hence excluded from meta-analysis. The combined sample size was 234 early/iAMD eyes and 221 normal eyes. The total MS mean difference was −1.47dB [−2, −0.94 dB], i.e., worsened, with a large and significant effect size (Z = 5.48, $p < 0.00001$). The estimates may have represented moderate to substantial heterogeneity and this was borderline statistically significant (I^2 = 55%, Chi^2 p = 0.03). As I^2 was ≥50%, individual study results were further investigated. Notable differences between the eight studies included different classifications of early/iAMD in almost every study and different testing radii and spatial areas analysed, likely contributing to the moderate-to-substantial heterogeneity. While all studies commonly reported decreased MS in early/iAMD (ranging from −0.5dB [−1.56, 0.56 dB] to −2.73dB [−4.62, −0.84 dB]), only three studies [#ID 13, 16, 17][91-93] reported statistically significant results.

Low-photopic and scotopic

Luu *et al*. [#ID 15][48] reported decreased MS which varied by AMD sub-group, using SAP (Medmont automated perimeter, 10° radius) under low-photopic conditions. The study compared 266 eyes with 'early AMD' (ICGS classification)[106] vs. 24 normal eyes and accounted for age. Three studies [#ID 12, 14, 15][15,48,100] also reported decreased MS using flicker perimetry (common 10° radius) under low-photopic conditions. These studies had varying sample sizes (15–266 early/iAMD eyes, 14 or 24 normal eyes), although ages were accounted for and AMD eyes were commonly defined by the ICGS classification.[106] Decreased MS were similar for the former two studies [#ID 12, 14][15,100] (−3.28dB [−3.82, −2.74 dB] and −4.09dB [−6.09, −2.09 dB], respectively), while the latter study [#ID 15][48] reported varying results by AMD sub-group.

Chen *et al*. [#ID 5][86] reported decreased MS (−2.73dB [−10.48, 5.02 dB]) using SAP (Octopus static automated perimeter, 25° radius and GV stimulus) under scotopic conditions using a Wratten blue filter (commercially available). Twenty-four eyes with 'dry-form age-related macular degeneration' were compared against normal eyes albeit without accounting for age differences.

Frequency of defects in early/intermediate age-related macular degeneration (iAMD) versus normal eyes

Photopic conditions

Two studies [#ID 1, 3][82,85] reported frequency of defects of early/iAMD eyes in comparison to normal eyes using SAP under photopic conditions (Supplementary *Table S4*). Sample sizes were slightly different (20 and 59 early/iAMD eyes, 22 and 15 normal eyes, respectively), both controlled or adjusted for age between groups, and testing conditions (10° radius) were similar. Both studies reported no significant mean difference in the frequency of defects.

Low-photopic conditions

Phipps *et al*. [#ID 22][49] reported significantly increased frequency of defects in early/iAMD eyes in comparison to normal eyes using SAP (Medmont automated perimeter, 10° radius) and flicker perimetry (10° radius) under low-photopic conditions. Twenty-five AMD eyes (modified ICGS classification)[106] were compared to 34 normal eyes with age accounted for. No studies explored frequency of defects under scotopic conditions.

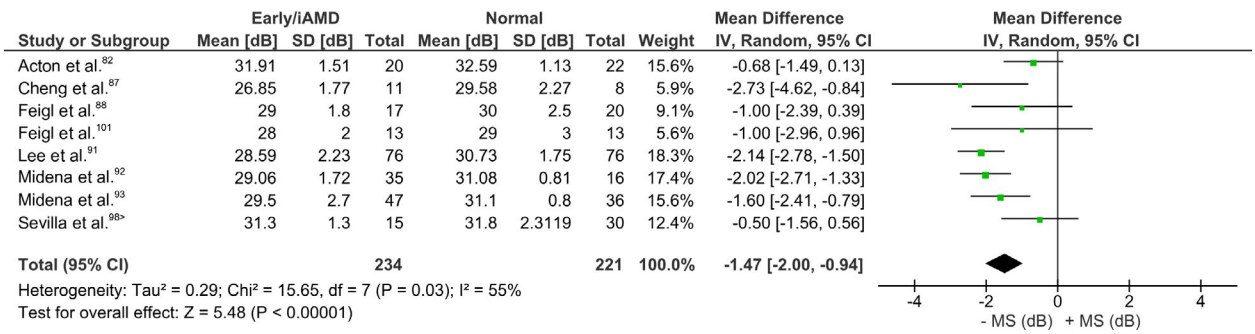

FIGURE 3 Forest plot of mean sensitivity (MS) mean differences between early/intermediate age-related macular degeneration (iAMD) and normal eyes using standard automated perimetry (SAP) under photopic conditions. Negative values indicate worsened MS in early/iAMD versus normal eyes

Dose-response gradient of visual field indices in early/intermediate age-related macular degeneration (iAMD) eyes

Several studies explored a potential dose-response gradient of visual field indices in early/iAMD eyes, i.e., whether indices worsened with increasing AMD severity. For MD (or equivalent), two studies [#ID 1, 26][82,97] using SAP under photopic conditions revealed no significant MD mean differences between different AMD stages, or between the 'worse eye' and 'better eye' of early/iAMD eyes, respectively. The former study compared 20 AMD eyes (Rotterdam study classification)[105] with 22 normal eyes using a 10° radius protocol, while the latter compared 66 AMD eyes (AREDS classification)[110] with 100 normal eyes using a 24–2 protocol. Both studies accounted for age between groups. No studies explored a dose-response gradient of MD (or equivalent) using low-photopic or scotopic conditions.

For PSD (or equivalent), Acton *et al*. [#ID 1][82] using SAP under photopic conditions found no significant PSD mean differences between different AMD stages. Study characteristics were as described above. No studies explored a dose-response gradient of PSD (or equivalent) using low-photopic or scotopic conditions.

For MS, four studies [#ID 1, 6, 16, 17][82,87,92,93] using SAP under photopic conditions reported varying dose-response relationships. The four studies had similar sample sizes (20 to 47 early/iAMD, 8 to 36 normal eyes) and testing protocol (common 10° radius). However, meta-analysis was not feasible due to the varying classifications of AMD, i.e., Rotterdam study,[107] 'PARM' and 'early ARM',[87] 'macular drusen'[92] and 'early AMD',[93] respectively. Three studies [#ID 1, 6, 17][82,87,93] revealed no significant differences in MS while Midena *et al*. [#ID 16][92] observed borderline decreased MS with increased AMD severity ('soft drusen' versus 'no soft drusen' and 'drusen size ≥63 μm' vs. <63 μm). Luu *et al*. [#ID 15][48] using SAP (Medmont automated perimetry, 10° radius) and flicker perimetry (10° radius) under low-photopic conditions described varying dose-response relationships as well. The sample size was 266 early/iAMD (ICGS classification)[106] and 24 normal eyes with age accounted for. Generally, there was significantly decreased MS with increased AMD severity, varying by the nine AMD subgroups. No studies explored a dose-response gradient of MS using scotopic conditions.

For frequency of defects, three studies [#ID 1, 4, 25][82,103,104] using SAP under photopic conditions reported relatively different dose-response relationships. Sample sizes varied (20 to 98 early/iAMD eyes, 22 normal eyes), AMD classifications varied (Rotterdam study,[107] AREDS,[105] and 'dry AMD', respectively) and testing protocol varied (10°, 10° radius, and 4° × 6° area, respectively). Meta-analysis was not feasible due to the varying classifications of AMD and insufficient outcome data. Two of the studies [#ID 1, 25][82,103] found no significant dose-response relationship, whereas Acton *et al*. [#ID 1][82] considered AMD staging and Tolentino *et al*. [#ID 24][103] considered drusen area as measures of AMD severity. Alternatively, Bharathi *et al*. [#ID 4][104] found a negative relationship between the frequency of defects and early/iAMD severity although with unclear significance, and Tolentino *et al*. [#ID 25][103] found a positive relationship when considering RPE atrophy area as a measure of AMD severity. No studies explored a dose-response gradient of frequency of defects using low-photopic or scotopic conditions.

Longitudinal global visual field indices in early/intermediate age-related macular degeneration (iAMD) eyes

Few studies explored longitudinal changes in visual field indices in early/iAMD eyes. There were no studies that reported MD (or equivalent), PSD (or equivalent) or frequency of defects over time. For MS, there were two studies [#ID 8, 10][101,102] using SAP under photopic conditions with different sample sizes (110 and 13 early/iAMD eyes, respectively) and AMD classifications (ICGS[106] and modified AREDS,[105] respectively), but identical testing protocol (10° radius) and follow-up time (one year). Both studies found no significant MS change over time. Owsley *et al*. [#ID 20][99] also used SAP under photopic conditions although reported a different MS outcome, i.e., baseline MS and AMD incidence over three years follow-up, and found no association. One study [#ID 15][48] assessed MS using SAP under low-photopic conditions and two studies [#ID 14, 15][48,100] assessed MS using flicker perimetry under low-photopic conditions. Most aspects of study designs were identical between study #14[100] and #15[48] (AMD ICGS classification,[106] 10° Medmont automated perimeter), except early/iAMD sample size (39 and 266 respectively) and follow-up time (two and one year, respectively). There was no significant MS change over time, except in one AMD sub-group where study #14[100] presented a greater rate of decreased MS in 'eyes that developed geographic atrophy' compared to normal eyes. No studies explored longitudinal changes in MS using scotopic conditions.

Secondary outcome – real-world patient outcomes

Only one study reported any real-world patient outcome in relation to the primary outcome. Wood *et al*. [#ID 26][97] investigated participants with early/iAMD using outcomes of SAP 24-2 under photopic conditions against on-road driving performance assessed by an occupational therapist. Measured outcomes for SAP included MD of the better and worse eye and 10° radius integrated visual fields (combined monocular visual fields including the more sensitive point-wise data). Measured outcome for on-road driving performance was an overall driver safety rating. There were no significant association of SAP outcomes compared to overall driver safety rating. Other outcomes for SAP

(e.g., Binocular Esterman score) and on-road driving performance (e.g., driving behaviours) were also assessed, although it is unclear whether these outcomes were directly compared.

DISCUSSION

This is the first systematic review including meta-analyses to explore the evidence regarding potential use of clinical automated perimetry in routine assessment of patients with early or iAMD. There was consistent evidence of significant visual field defects in early/iAMD compared to normal eyes under photopic, low-photopic and scotopic conditions. However, meta-analyses demonstrated that reductions in global visual field indices at least using SAP under photopic conditions were not clinically meaningful, while there was insufficient data to draw conclusions regarding other clinical automated perimetry protocols. There was also a dearth of evidence translating early/iAMD visual field outcomes to real-world patient findings, highlighting the need for more studies in this area. Thus, SAP under photopic conditions is unlikely to be useful for routine assessment of early/iAMD.

Standard automated perimetry (SAP) under photopic conditions is inadequate for routine clinical assessment of age-related macular degeneration (AMD)

In this review, we provide the first meta-analyses addressing whether global visual field indices measured using clinical automated perimetry are impacted in early/iAMD. MD, PSD and MS were consistently worse in early/iAMD compared to normal eyes across the different visual field testing protocol and lighting conditions, despite possible moderate to substantial heterogeneity between studies. The summary outcomes of −1.52dB MD and −1.47dB MS using SAP under photopic conditions in early/iAMD compared to normal eyes, however, did not equate to a clinically meaningful effect size[79,111,112] when considering the magnitude of SAP test-retest variability in normal eyes up to (one standard deviation) ±2.5dB MD[58,113,114,115,116] and ±2dB MS.[35,59,116,117,118] Regarding PSD mean difference in early/iAMD eyes compared to normals, studies using SAP under photopic conditions reported mixed outcomes, and PSD magnitudes were also small when considering test-retest variability up to ±1.5dB PSD.[58,113,114,115,116] Our results demonstrate that the magnitude of global visual field indices in early/iAMD using SAP under photopic conditions do not provide clinically meaningful results.

It has been well-recognised that the relationship between visual field sensitivity and background luminance is represented by the threshold-versus-intensity (TVI) function.[119,120] In diseases that primarily cause photoreceptor impairment such as AMD,[2] the TVI function shifts 'upwards and rightwards'.[121-124] Thus, there is a greater disparity in increment threshold (and thus visual field sensitivity) between normal and photoreceptor-diseased eyes under lower light conditions.[121-123] Empirically, studies have long established psychophysical evidence for visual field testing under lower light conditions in AMD eyes,[125-130] as previously modelled.[131,132]

In this review, there were an inadequate number of studies utilising flicker perimetry or FDT, and low-photopic or scotopic lighting conditions to amalgamate into meta-analyses. General results indicated worsened global visual field indices in early/iAMD eyes that underwent the testing protocol, although no substantial conclusion(s) could be drawn regarding their role for routine functional assessment of early/iAMD. Conversely, there is increasing microperimetry use (which operates under lower light conditions than most SAP) for macular disease research. Studies using microperimetry have ostensibly evinced greater magnitude of worsened global visual field indices in early/iAMD eyes[133-141] compared to the results we describe under photopic conditions. However, the lack of systematic evidence addressing whether microperimetry may be useful for routine functional assessment of AMD in clinic warrants further review.

Paucity of evidence denoting a cause-effect relationship between early/intermediate age-related macular degeneration (iAMD) and visual field outcomes

Another consideration in establishing the potential use of visual fields for routine assessment of early/iAMD is whether there is an apparent cause-effect relationship. A putative cause-effect relationship may be strengthened by demonstration of a dose-response gradient and temporal relationship.[142] That is, is there evidence that global visual field indices in early/iAMD eyes worsen as a function of disease severity and time? For example, these relationships are fundamental to the integration of visual field testing in glaucoma clinical staging[143] and monitoring.[144,145]

Overall, dose-response gradients from the studies in this review formed equivocal results. MD, PSD and frequency of defects in relation to AMD severity showed no dose-response using SAP under photopic conditions. Meanwhile, some studies revealed worsened MS with increased AMD severity[48,92] while others did not[82,87,93] using SAP, likely due to differing definitions of AMD severity and also differing visual field testing conditions. Because of these highly variable outcomes, further studies using standardised AMD classification and results that are more transparent are needed to ascertain whether there may be a dose-response relationship that would help support the cause-effect relationship between visual field defects and AMD.

Evidence for a longitudinal relationship between early/iAMD and global visual field indices were also mostly equivocal. MS did not change over follow-up periods up

to two years using SAP under photopic or low-photopic conditions, or flicker perimetry under low-photopic conditions. Notably, however, Luu *et al*.[100] using flicker perimetry under low-photopic conditions highlighted that AMD 'eyes that developed geographic atrophy' (GA) had a significantly faster rate of decreasing MS than normal eyes. When considering only locations that developed GA, rate of decreasing MS was faster than both normal and 'high-risk early AMD' eyes (i.e., 'early AMD' eyes that did not develop late AMD). These changes were not found in AMD 'eyes that developed neovascularisation'. These data suggest a possible monitoring/prognostic role for flicker perimetry in clinical settings, as AMD eyes that have faster deteriorating MS may be indicative of oncoming GA. At the time of Luu *et al*'s[100] publication, structural biomarkers including incomplete retinal pigment epithelial and outer retinal atrophy[146] which overlaps with the definition of nascent GA[147,148] had not yet been described. It is possible that the faster progressing areas that Luu *et al*.[100] described via flicker perimetry may correlate to the aforementioned structural biomarkers. Future study detailing structure-function correlations in early/iAMD eyes would help clarify this uncertainty. Overall, while a majority of longitudinal studies exhibited no significant visual field changes in early/iAMD eyes, the duration of follow-up was insufficient considering the protracted natural history of AMD.[109] Longer duration cohort studies are needed to establish whether automated perimetry may be useful for clinical monitoring of AMD.

Dearth of evidence translating early/intermediate age-related macular degeneration (iAMD) visual field outcomes to real-world patient outcomes

Recent studies have demonstrated a linkage between early/iAMD and real-world patient outcomes.[149-152] Correspondingly, there is growing interest in determining which visual function tests (with or without structural tests) may best reflect patients' quality of life and daily living activities. Surprisingly though, only one study met these eligibility criteria in this review and addressed whether visual field outcomes in early/iAMD linked to real-world patient outcomes, and found no link between global visual field indices and driving safety. During the literature search, another study[153] was identified which described links between global visual field indices and parts of the Turkish National Eye Institute-Visual Function Questionnaire-25 describing various quality of life factors, e.g., near and distance activities, vision-specific social functioning and mental health, etc. However, no relevant comparison group was included and hence this study was excluded from our results. There is hence ample opportunity for future studies to explore whether using automated perimetry in patients with early/iAMD can effectively translate into patient outcomes. Establishing this link is vital not just when considering if visual field testing can improve patient outcomes, but also as patient compliance to clinician advice significantly improves with better patient understanding of how their disease may impact upon vision.[154,155]

Future directions

Synthesis of the literature for this review uncovered a diverse quality and high risk of bias in all studies, making critical appraisal challenging. To overcome this, we used a highly recognised quality assessment[28,66] and risk of bias assessment guides,[71,72] included meta-analysis where possible, and also provided comprehensive tables of relevant data for transparency. Inclusion of our systematic review into a formal register such as PROSPERO could have also helped to mitigate repeated efforts and reporting bias, and promoted transparency.[156]

Analysis of observational studies also includes inherent biases due to differences in inter-study designs and populations which lack experimental randomisation.[157] In future, test accuracy can be improved by consecutive or random enrolment of participants,[158,159] which would be more representative of populations the clinician would encounter in routine clinical practice.[27] Additionally, more consistency in reporting would benefit future syntheses of data. Consistently reported measures such as exact AMD classification, visual field testing conditions, statistical significance and inclusion of dose-response and temporal relationships where possible would strengthen the putative cause-effect relationship between early/iAMD and visual field defects. More stringent reporting of funding and conflict of interest statements would also help ascertain the risk of sponsorship bias.[70,160,161,162] Admittedly, some reporting uncertainties could have been clarified through contact of the study authors and improved our review credibility.[163] It is however unlikely that this would have made a significant impact on our mostly negative findings and conclusions.

This review also highlighted that while current clinical automated perimetry may reveal functional deficits in early/iAMD, more sensitive functional testing than SAP under photopic conditions is required to confer clinical significance. Studies using low-photopic or scotopic light conditions that we reviewed along with other studies[133-141] using microperimetry that operates under borderline low-photopic/mesopic lighting conditions (1.27 cd/m^2)[33,34] have demonstrated greater magnitude of worsened global visual field indices in early/iAMD eyes compared to the majority of our results, which represent photopic conditions. This begets the question of whether current clinical automated perimetry, which can already operate at lower light conditions, could produce similar results to microperimetry.

Finally, sparingly discussed in the literature is the advantage of topographical, visual function description provided via automated perimetry. From the 26 studies included, only four[#ID 1, 5, 12, 15][15,48,82,86] reported global visual field indices with respect to eccentricity. These

four studies commonly reported less decreased MD or MS with increasing eccentricity using SAP and/or flicker perimetry. This common topographical pattern of visual field change may suggest structure-function linkage, as drusen occur most commonly towards the central macula.[164,165] Considering the growing body of evidence highlighting the structure-function relationship in early/iAMD,[98,133,134,136,138,140,141,166–174] automated perimetry may still have potential for clinical integration (albeit not using SAP under photopic conditions) to fortify diagnoses and monitoring of disease, akin to its role for glaucoma.[175] There may also be a use for automated perimetry as a functional biomarker for pre- and post-treatment of late stage AMD. However, demonstration of benefit to patient outcomes in lower-risk early/intermediate, treatment-naïve AMD patients is necessary before imposing more testing burden on these individuals.

CONCLUSION

There was consistent evidence of significant visual field defects in early/iAMD compared to normal eyes under photopic, low-photopic and scotopic conditions. However, meta-analyses results demonstrated that global visual field index reductions at least using SAP under photopic conditions were not clinically meaningful, while there was insufficient data to draw conclusions regarding other clinical automated perimetry protocols. Evidence regarding translational relevance of visual field findings to patient outcomes is lacking and should be considered. Thus, SAP under photopic conditions is unlikely to be useful for the routine assessment of early/iAMD.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article. The sources of funding were not involved in any aspects of study design or conduct.

AUTHOR CONTRIBUTION

Matt Trinh: Conceptualization (equal); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Validation (lead); Visualization (lead); Writing-original draft (lead); Writing-review & editing (lead). **Michael Kalloniatis:** Conceptualization (equal); Funding acquisition (supporting); Project administration (supporting); Resources (supporting); Software (supporting); Supervision (supporting); Visualization (supporting); Writing-review & editing (supporting). **Lisa Nivison-Smith:** Conceptualization (equal); Formal analysis (supporting); Funding acquisition (lead); Methodology (supporting); Project administration (lead); Resources (lead); Software (lead); Supervision (lead); Validation (supporting); Visualization (supporting); Writing-original draft (supporting); Writing-review & editing (supporting).

ORCID

Matt Trinh https://orcid.org/0000-0002-6184-0666
Michael Kalloniatis https://orcid.org/0000-0002-5264-4639
Lisa Nivison-Smith https://orcid.org/0000-0001-6677-1949

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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