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Screening for Impaired Visual Acuity in Older Adults: A Systematic Review for the U.S. Preventive Services Task Force

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Table of Contents

Chapter 1. Introduction and Background	1
Purpose.....	1
Condition Background.....	1
Condition Definition.....	1
Prevalence and Burden of Disease/Illness.....	2
Etiology and Natural History.....	4
Risk Factors.....	5
Rationale for Screening/Screening Strategies.....	5
Interventions/Treatment.....	6
Current Clinical Practice/Recommendations of Other Groups.....	7
Chapter 2. Methods	8
Key Questions and Analytic Framework.....	8
Search Strategies.....	8
Study Selection.....	9
Data Abstraction and Quality Rating.....	9
Data Synthesis and Analysis.....	9
USPSTF Involvement.....	10
Expert Review and Public Comment.....	10
Chapter 3. Results	11
Key Question 1. What are the effects of vision screening in asymptomatic older adults versus no screening on visual acuity, morbidity or mortality, general or vision-related quality of life, functional status, or cognition?.....	11
Summary.....	11
Evidence.....	11
Key Question 2. What are the harms of vision screening in asymptomatic older adults versus no screening?.....	13
Summary.....	13
Evidence.....	13
Key Question 3. What is the diagnostic accuracy of screening for impaired visual acuity due to uncorrected refractive error, cataracts, or AMD?.....	13
Summary.....	13
Evidence.....	14
Key Question 4. What is the accuracy of instruments for identifying patients at higher risk of impaired visual acuity due to uncorrected refractive error, cataracts, or AMD?.....	17
Summary.....	17
Evidence.....	17
Key Question 5. What are the effects of treatment for wet or dry AMD versus placebo or no treatment on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?.....	18
Summary.....	18
Evidence.....	19
Key Question 6. What are the effects of newer (aflibercept or brolocizumab-dbll) versus older VEGF inhibitors for wet AMD on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?.....	24

Summary.....	24
Evidence.....	24
Key Question 7. What are the harms of treatment for early impaired visual acuity due to wet or dry AMD?	26
Summary.....	26
Evidence.....	27
Chapter 4. Discussion	29
Summary of Review Findings	29
Limitations	31
Emerging Issues/Next Steps	31
Relevance for Priority Populations	32
Future Research	32
Conclusions.....	33
References	34

Figures

- Figure 1. Analytic Framework and Key Questions
- Figure 2. ≥ 15 Letters of Visual Acuity Gain With Use of VEGF Inhibitors at 1-Year Followup
- Figure 3. < 15 Letters of Visual Acuity Loss With Use of VEGF Inhibitors at 1-Year Followup
- Figure 4. Visual Acuity of 20/200 or Better With Use of VEGF Inhibitors at 1-Year Followup

Tables

- Table 1. Measurements of Visual Acuity
- Table 2. Recommendations of Other Groups
- Table 3. Trials of Vision Screening
- Table 4. Summary of Evidence

Appendixes

Appendix A. Detailed Methods

- Appendix A1. Search Strategies
- Appendix A2. Inclusion and Exclusion Criteria
- Appendix A3. Literature Flow Diagram
- Appendix A4. Included Studies
- Appendix A5. Excluded Studies
- Appendix A6. U.S. Preventive Services Task Force Quality Rating Criteria
- Appendix A7. Reviewers of the Draft Report

Appendix B. Evidence Tables and Quality Tables

- Appendix B Table 1. Trials of Vision Screening
- Appendix B Table 2. Trials of Vision Screening, Quality Assessment
- Appendix B Table 3. Diagnostic Accuracy of Vision Screening Tests, Study Characteristics
- Appendix B Table 4. Diagnostic Accuracy of Vision Screening Tests, Results
- Appendix B Table 5. Diagnostic Accuracy of Vision Screening Tests, Quality Assessment
- Appendix B Table 6. Diagnostic Accuracy of Vision Screening Instruments, Study Characteristics
- Appendix B Table 7. Diagnostic Accuracy of Vision Screening Instruments, Quality Assessments

Appendix B Table 8. Diagnostic Accuracy of Vision Screening Instruments, Results
Appendix B Table 9. Trials of VEGF Inhibitors
Appendix B Table 10. Trials of VEGF Inhibitors, Quality Assessment
Appendix B Table 11. AREDS Trials of Multivitamins
Appendix B Table 12. AREDS Trials of Multivitamins, Quality Assessment
Appendix B Table 13. Systematic Review of Multivitamins
Appendix B Table 14. Systematic Review of Multivitamins, Quality Assessment
Appendix B Table 15. Additional Trials of Multivitamins
Appendix B Table 16. Additional Trials of Multivitamins, Quality Assessment
Appendix B Table 17. Trials of Multivitamins, Harms

Structured Abstract

Background: In 2016, the United States Preventive Services Task Force (USPSTF) concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for impaired visual acuity in older adults (**I Statement**). Although the USPSTF found that screening can identify persons with impaired visual acuity and that effective treatments are available for common causes of impaired visual acuity, direct evidence found no differences between vision screening versus no screening on visual acuity or other clinical outcomes.

Purpose: To systematically review the evidence on screening for impaired visual acuity in older adults for populations and settings relevant to primary care in the United States.

Data Sources: We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and MEDLINE (through February 9, 2021), reviewed the studies in the prior USPSTF report, and manually reviewed reference lists.

Study Selection: Randomized controlled trials (RCTs) and controlled observational studies on benefits and harms of screening versus no screening; studies on diagnostic accuracy of screening tests and instruments (including questionnaires); and benefits and harms of vascular endothelial growth factor (VEGF) inhibitors for wet age-related macular degeneration (AMD) and antioxidant vitamins and minerals for dry AMD in adults age 65 years and older.

Data Extraction: One investigator abstracted data and a second checked accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): A total of 25 studies were included in this review (13 trials, 11 diagnostic accuracy studies, and one systematic review [of 19 trials]). Sixteen studies were carried forward from the 2016 review for the USPSTF, eight studies were new, and the systematic review utilized in the 2016 review for the USPSTF was updated to include six new trials.

Four trials (N=4,819) of screening versus no screening, usual care, or delayed screening of older adults found no differences in visual acuity or other clinical outcomes. Visual acuity tests (3 studies; N=6,493) were associated with suboptimal diagnostic accuracy for identifying visual conditions compared with a complete examination by an ophthalmologist (sensitivity 0.27 to 0.75 and specificity 0.51 to 0.87); evidence on other screening tests was limited. Three studies (N=5,203) found that a screening question was not accurate for identifying older persons with impaired visual acuity compared with a visual acuity eye chart (sensitivity 0.17 to 0.81 and specificity 0.19 to 0.84).

For wet AMD, four trials (N=2,086) found VEGF inhibitors associated with greater likelihood of ≥ 15 letters (3 lines) of visual acuity gain (risk ratio [RR] 2.92, 95% confidence interval [CI] 1.20 to 7.12, $I^2=76\%$; absolute risk difference [ARD] 10%), < 15 letters (3 lines) of visual acuity loss (RR 1.46, 95% CI 1.22 to 1.75, $I^2=80\%$; ARD 27%) and having vision 20/200 or better (RR 1.47, 95% CI, 1.30 to 1.66, $I^2=42\%$; ARD 24%) at 1 year versus sham injection. VEGF inhibitors were associated with better vision-related function and quality of life measures versus

sham injection at 1 and 2 years, the difference (~8 points on a 0 to 100 scale) was above the minimum clinically important difference threshold.

For dry AMD, a systematic review of 19 trials found antioxidant multivitamins associated with decreased risk of progression to late AMD (3 trials, N=2,445 people, odds ratio [OR] 0.72, 95% CI 0.58 to 0.90) and ≥ 3 lines visual acuity loss (1 trial, N=1,791 people, OR 0.77, 95% CI 0.62 to 0.96) versus placebo. Results were primarily driven by the large (n=3,640) Age-Related Eye Disease Study (AREDS). Zinc was associated with decreased risk of progression to late AMD versus placebo (3 trials, N=3,790 people, OR 0.83, 95% CI 0.70 to 0.98) and decreased risk of ≥ 3 lines visual acuity loss that was of borderline statistical significance (2 trials, 3,791 people, RR 0.87, 95% CI 0.75 to 1.00). Evidence on the effects of other vitamins and mineral treatments was limited or showed no clear effects on AMD progression or visual acuity. The AREDS trial found zinc use associated with increased risk for hospitalization due to genitourinary causes versus nonuse (7.5% vs. 4.9%, RR, 1.47, 95% CI, 1.19 to 1.80); other serious harms were infrequent, with no differences between groups. The AREDS 2 trial found the AREDS formulation with beta carotene associated with increased risk of lung cancer versus the AREDS formulation without beta carotene when current smokers were excluded from the analysis (2.0% vs. 0.9%, p=0.04); almost all lung cancers occurred in former smokers.

Limitations: Screening trials had methodological limitations that could have attenuated potential benefits; utilized an update to a previously included systematic review on antioxidant multivitamins and minerals for dry AMD; evidence on the effectiveness of treatment for dry AMD relied heavily on results of a single trial (AREDS); non-English-language studies excluded; too few randomized trials to perform formal assessments for publication bias with graphical or statistical methods for small sample effects; statistical heterogeneity in pooled estimates for VEGF inhibitors versus sham, though inconsistency was in magnitude (not direction) of effect.

Conclusions: Impaired visual acuity is common in older adults and effective treatments are available for common causes of impaired visual acuity. Visual acuity testing is the reference standard for identifying impaired visual acuity, but has low diagnostic accuracy compared with an ophthalmological exam for identifying visual conditions not necessarily associated with impaired visual acuity; screening questions have low diagnostic accuracy compared with visual acuity testing. Direct evidence found no significant difference between vision screening in older adults in primary care settings versus no screening in visual acuity-related outcomes or other clinical outcomes.

Chapter 1. Introduction and Background

Purpose

This report updates a 2016 review for the U.S. Preventive Services Task Force (USPSTF)^{1,2} on screening for impaired visual acuity in older adults (defined as persons 65 years of age or older). It will be used by the USPSTF to update its 2016 recommendation.³ In 2016, the Task Force concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for impaired visual acuity in older adults (**I Statement**). Although the prior USPSTF review found that screening can identify persons with impaired visual acuity and that effective treatments are available for common causes of impaired visual acuity, direct evidence found no significant difference between vision screening in older adults in primary care settings versus no screening in visual acuity or other clinical outcomes.

This review focuses on screening for and treatment of impaired visual acuity associated with the following conditions: uncorrected refractive errors, cataracts, and age-related macular degeneration (AMD). This review does not address screening for diabetic retinopathy. Screening for diabetic retinopathy is not addressed by the USPSTF, as it is considered part of diabetes follow up and management (screening for diabetes is addressed elsewhere by the USPSTF).⁴ For this review, we use the term “impaired visual acuity” rather than “vision impairment” because the latter term implies functional limitations, which may or may not be present. In addition, vision impairment can occur for reasons other than visual acuity loss. For the purposes of this review, “asymptomatic” individuals are defined as those without known impaired visual acuity (based on current corrected vision) who have not sought care for evaluation of vision problems.

Condition Background

Condition Definition

Impaired visual acuity refers to decreased clarity or sharpness of vision. In addition to decreased or substandard visual acuity, uncorrected impaired visual acuity can also be associated with decreases in lowlight vision, color vision, binocularity, contrast sensitivity, accommodation, or stereopsis, as well as visual field loss (areas in the field of view in which objects cannot be seen). Visual acuity is most commonly determined in primary care settings using a tool such as the Snellen or Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, which assess high contrast visual acuity based on the ability of patients to recognize letters of different sizes arranged in rows from a prespecified distance (typically 20 feet). Roughly speaking, a person with 20/100 vision according to a visual acuity chart would need to be 20 feet away to read the smallest letters that someone with “normal” (20/20) vision could read at 100 feet. Visual acuity can also be described in meters (6/6 in meters is equivalent to 20/20 in feet) or using the decimal or the logarithm of the minimum angle of resolution (logMAR) scale (**Table 1**). The severity of decreased visual acuity varies. Impaired visual acuity has been defined as visual acuity of worse than 20/40⁵ or 20/50⁶ but better than 20/200 (the threshold for legal blindness). This definition

for impaired visual acuity was used in this report, unless otherwise noted. Visual acuity can be measured with or without refractive correction; for the purposes of this review, impaired visual acuity refers to current corrected visual acuity.

High contrast visual acuity worse than 20/20 but better than 20/40 is generally thought to have minimal effects on reading ability, functional capacity, or quality of life. In the United States (U.S.), the visual acuity standard for driving without restrictions is 20/40 or better. Although the International Council of Ophthalmology defined mild impaired visual acuity in 2002 as worse than 20/25 and better than 20/80,⁷ some studies have used a definition for mild impaired visual acuity of between roughly 20/40 and 20/80.^{5,6} This degree of impaired visual acuity is less likely to cause major functional limitations than more severe impairment, and may be more apt to be unidentified without screening. Although these criteria focus on findings for high contrast visual acuity, normal high contrast visual acuity can be associated with decreased low contrast visual acuity and contrast sensitivity.⁸ As described in a Contextual Question in the prior USPSTF review, definitions for a clinically important change in visual acuity vary across studies. However, a difference of at least 15 letters (equivalent to three lines on the ETDRS), representative of a doubling of the visual angle, is a commonly reported outcome in studies assessing visual acuity.^{9,10}

AMD, cataracts, refractive errors, and presbyopia are common causes of impaired visual acuity in older adults. AMD leads to blurred vision and development of scotomas that obscure central vision. AMD is the leading cause of legal blindness for persons older than age 65 years. Atrophic or “dry” (nonexudative) macular degeneration accounts for 85 to 90 percent of AMD cases. Although AMD becomes “wet” (exudative or neovascular) in only 10 to 15 percent of cases, wet AMD accounts for over 80 percent of cases of severe visual loss from AMD.¹¹ Cataracts lead to blurring of vision, increased sensitivity to glare, and loss of sensitivity to differences in contrast. Refractive errors, such as myopia (nearsightedness) or hyperopia (farsightedness), occur when the eye is unable to bring parallel rays of light into focus on the fovea.¹² Presbyopia, which occurs as part of the natural aging process of the eye, is the loss of the eye’s ability to change its focus to see objects that are near. This occurs as the eyes’ lenses begin to lose flexibility around age 45 years, and affects most people at some point in life.

Prevalence and Burden of Disease/Illness

In 2015, of 3.22 million persons with visual impairment, approximately half were persons ages 80 years and older, 24 percent were 70 to 79 years of age, and 16 percent were 60 to 69 years of age.¹³ The prevalence of impaired visual acuity rises significantly with age in older adults, from 1.1 percent in persons ages 65 to 69 years to 16.7 percent in persons older than age 80 years,¹⁴ and the prevalence of both blindness and impaired visual acuity increases with age, especially among people age 80 years and older.^{13,15} The number of persons age 60 years and older with impaired visual acuity (defined as visual acuity worse than 20/40 but better than 20/200) was estimated at 2.91 million in 2015 and the number blind (defined as visual acuity 20/200 or worse) was estimated at 0.76 million.¹³ These numbers were projected to increase to 6.57 and 1.73, respectively, in 2050, due to the aging of the population. The prevalence of specific causes of impaired visual acuity (i.e., AMD, cataracts, refractive errors, and presbyopia) is described

below. The cost of impaired visual acuity and blindness to the U.S. economy is estimated at \$5.48 billion.^{16,17}

Age-Related Macular Degeneration

The prevalence of AMD in the 2005 to 2008 National Health and Nutrition Examination Survey was 6.5 percent in persons older than age 40 years (estimated 7.2 million individuals in the U.S.) and increased with age (2.8% in ages 40 to 59 years and 11.1% in age ≥ 60 years).¹⁸ The prevalence of early AMD was 5.7 percent, late AMD 0.8 percent, wet (exudative) AMD 0.3 percent, and advanced dry AMD (geographic atrophy) 0.5 percent. AMD is more common among White non-Latino and Latino persons compared to Black persons, especially among the very old (≥ 75 years).^{18,19} The prevalence of AMD in males and females is similar.

Cataracts

Cataracts are the cause of low vision (defined as best-corrected visual acuity worse than 20/40) in approximately half of cases.²⁰ The prevalence of cataracts increases sharply with age. Approximately 22 million U.S. adults age 40 years and older were estimated to have cataracts (not necessarily associated with vision impairment) in 2011,²¹ and 50 percent of those age 80 years and older are estimated to have cataracts. In White females, prevalence increases from 27.7 percent in ages 65 to 69 years to 76.6 percent in those age 80 years or older. In Black females, respective prevalence rates are 28.5 and 60.9 percent, in White males they are 22.4 and 71.3 percent, and in Black males they are 17.5 and 46.2 percent.

Refractive Errors

Refractive errors are the most common cause of impaired visual acuity in the U.S. and worldwide. In older adults with impaired visual acuity due to hyperopia or myopia (including those currently using corrective lenses), approximately 60 percent have correctable (to better than 20/40) refractive errors.⁶ In general, the prevalence of hyperopia increases sharply with age, with a prevalence that is 4.2 to 7.4 times higher in persons age 80 years or older compared to those ages 40 to 49 years.^{12,19} The prevalence of hyperopia requiring a correction of +3.0 diopters (D) or more (at least moderate severity) ranges is about 5.9 percent in U.S. adults ages 50 to 54 years, 15.2 percent in adults ages 65 to 69 years, and 20.4 percent in adults age 80 years and older. At any age, hyperopia is more common in White non-Latino persons than Black or Latino persons, and is also more prevalent in females than males. For example, among White males, the prevalence of hyperopia of +3.0 D or more is 3.6 percent among those ages 40 to 49 years, 14.1 percent among those ages 65 to 69 years, and 23.5 percent among those older than 80 years. Respective rates for White females are 3.7, 17.8, and 27.2 percent, and for Black females they are 3.1, 10.6, and 13.5 percent. An exception to increasing prevalence of hyperopia with age is adult Black males, in whom the prevalence of hyperopia remains fairly constant across age groups, ranging from 1.5 to 3.9 percent.¹²

Among adults older than age 65 years, the prevalence of myopia is relatively stable with increasing age, though prevalence varies among different ethnic/racial groups. For example, the prevalence of myopia of at least -1.0 D in Black males ages 65 to 69 years is 8.1 percent

compared with 13.1 percent in Latino males and 17.7 percent in non-Latino white males.¹² The prevalence of myopia of at least -1.0 D tends to decrease with age from about 25.7 percent in U.S. adults ages 50 to 54 years, to 16.0 percent in adults ages 65 to 69 years and 17.5 percent in adults age 80 years and older. At any age, myopia is more prevalent in non-Latino White persons than Black or Latino persons.

It is estimated that around three-quarters of U.S. individuals with impaired visual acuity due to uncorrected refractive error could experience improvement with proper refractive correction.¹³

Presbyopia

The prevalence of presbyopia, or age-related loss of accommodation, increases with age and affects most people at some point in life. The onset of presbyopia generally occurs around age 45 years, though onset tends to be somewhat earlier in people who live in areas with higher ambient temperatures.²²

Regardless of its cause, impaired visual acuity is consistently associated with decreased functional capacity and quality of life in older people, including the ability to live independently, with more severe impaired visual acuity associated with greater negative effects.²³⁻²⁷ Impaired visual acuity can affect ability to perform both basic and instrumental activities of daily living, work, drive safely, or obtain a driver's license, as well as increase risk of falls and other accidental injuries.²⁸⁻³² However, there is inter-individual variability in the degree of functional impairment in persons with the same degree of impaired visual acuity. Vision loss is also associated with higher prevalence of depression and social isolation.^{24,33} Of older adults experiencing impaired visual acuity, 57.2 percent are at risk for mild or moderate depression compared to 43.5 percent of those without vision loss.³⁴ When combined with other chronic health conditions, vision loss is associated with overall poorer health among people age 65 years and older.¹⁵

According to the Centers for Disease Control and Prevention, an estimated 61 million U.S. adults are at high risk for serious vision loss, which can cause a substantial social and economic toll, including disability, loss of productivity, and reduced quality of life.³⁵ Experts predict that by 2030, rates of severe vision loss will double or triple as the aging population increases³⁴⁻³⁶ and the number of older adults (age ≥ 65 years) increases.^{15,24,34,37} Direct medical expenses for older adults with impaired visual acuity in the U.S. are \$8.3 billion annually,¹⁵ including an estimated annual \$6.8 billion for cataract treatment.³⁸

Etiology and Natural History

Refractive errors are a general term to describe conditions associated with the inability of the cornea and lens of the eye to bring parallel rays of light into sharp focus on the fovea, resulting in blurry vision. In adults, common types of refractive errors are myopia, hyperopia, and astigmatism. Myopia occurs when images are focused in front of the fovea, affecting ability to clearly view more distant objects.³⁹ Hyperopia occurs when images are focused behind the fovea, which affects the ability to sharply view closer objects. Hyperopia often presents or worsens with older age due to presbyopia, which refers to age-related changes in the eye, including decreased

elasticity of the lens, reducing near-focusing ability. Astigmatism is a condition in which there are two or more focal points in the eye, resulting in distortion of images at various distances. Progression of myopia in older adults can be associated with development and progression of cataracts. Cataracts are opacities in the lens of the eye, which generally progress over time and result in decreased visual acuity and glare.⁴⁰

AMD affects the macula, the area of the retina responsible for central vision.⁴¹ Drusen, which are white to yellow retinal lesions, are an early sign of AMD when they occur in the macula. Early stage AMD with small to medium-sized drusen and no pigment change is not associated with vision loss. However, about one to three out of 100 people with small drusen experience vision problems within five years, and about 50 out of 100 people with larger drusen develop advanced AMD and vision loss within five years.⁴² Advanced AMD is usually classified into “wet” or “dry” forms. The dry form of advanced AMD (also referred to as “geographic atrophy”) is more common and associated with atrophy of the retinal layers and retinal pigmented epithelial cells. The wet form of AMD is associated with the development of abnormal blood vessels in the choroid layer underneath the retina (choroidal neovascularization). Both types of advanced AMD can cause blurred central vision, distorted vision, and decreased lowlight vision. Dry AMD progresses more gradually than wet AMD, and is less likely to cause vision loss or other vision problems, though dry AMD can turn into wet AMD. In severe cases, advanced AMD results in central scotomas (complete loss of central vision).

Risk Factors

The prevalence of impaired visual acuity is higher among people of lower socioeconomic or educational status and those without private health insurance.^{6,12} Risk factors for impaired visual acuity vary depending on the specific condition. A positive family history is a major risk factor for both myopia and hyperopia.³⁹ In both sexes and in various ethnic/racial groups, latent hyperopia tends to manifest with older age due to a loss in accommodation, with the exception of Black men, in whom the prevalence of hyperopia remains relatively low.¹² Risk factors for cataracts include older age, smoking, alcohol use, exposure to ultraviolet light, eye trauma, ocular inflammatory diseases, diabetes, and exposure to corticosteroids.^{43,44} Lower socioeconomic status and Black race are associated with higher rates of unoperated cataracts.⁴⁵ Risk factors for AMD are not completely understood, but are thought to include older age, smoking, obesity, diet, elevated cholesterol, cardiovascular disease, and family history.^{46,47} AMD is more common in White persons compared to other races/ethnicities.¹²

The Behavioral Risk Factor Surveillance System Vision Impairment Expert Panel concluded that the most substantial barriers to vision preventive care, treatment, and rehabilitation appear to be behavioral issues, followed by cost and geographic access. Behavioral and cultural issues include patient belief systems, trust issues, education and language barriers, health literacy issues, immigration status, and concordance between doctor and patient.⁴⁸

Rationale for Screening/Screening Strategies

Impaired visual acuity due to uncorrected refractive error, cataracts, and AMD is common in

adults and the prevalence increases with age.^{12,49,50} Impaired visual acuity in older adults may not be recognized or may remain unreported because vision changes can be relatively subtle, occur in more advanced stages of the condition, progress slowly over time, occur in persons with cognitive dysfunction or other comorbid conditions. However, even mildly impaired visual acuity may be associated with decreased quality of life and functional capacity and increased likelihood of accidents and related injuries.^{23,25-27} In addition, vision loss due to AMD may be irreversible. Screening provides an opportunity to address disparities in detection and treatment of impaired visual acuity among racial/ethnic groups, and targeting older adults addresses the population most likely to be affected. Screening for impaired visual acuity in the primary care setting is noninvasive and could potentially identify persons without access to specialty eye services likely to benefit from referral for interventions to improve visual acuity, slow progression of ocular disease, or prevent the development of irreversible vision loss.²

Interventions/Treatment

A number of interventions are available to treat common causes of impaired visual acuity. Although impaired visual acuity may be identified in the primary care setting, most interventions require the involvement of an eye care provider. Presbyopia is often corrected with prescription glasses, contact lenses, reading glasses, progressive addition lenses, or bifocals. Refractive errors may be remedied with corrective lenses, contact lenses, or refractive surgery. Photorefractive surgery (including laser in situ keratomileusis, photorefractive keratectomy, or laser epithelial keratomileusis) is associated with more upfront costs compared to corrective lenses and more commonly selected as a treatment option by younger adults. Older patients undergoing photorefractive surgery may be slightly less likely to experience optimal results and slightly more likely to need repeat treatment or enhancement compared with those younger.⁵¹

For patients with impaired visual acuity that is not sufficiently improved by correcting refractive error and in whom other treatable causes cannot be identified, reading aids (such as magnifiers) are a treatment option.⁵² For cataracts causing significant impairment in visual acuity, the most common treatment is surgical cataract extraction and intraocular lens implantation.⁵³ Cataract surgery is effective in improving vision in 90 percent of patients, has a low complication rate, generally can be performed as an outpatient procedure, and can restore vision even in patients with advanced cataracts.⁵⁴

Antioxidants and vitamins are used to slow progression of dry AMD, but have no proven benefit in slowing cataract progression.⁵⁵⁻⁵⁸ No treatment is known to reverse the retinal damage associated with dry AMD. The wet form of AMD accounts for most of the vision loss and blindness associated with advanced AMD. For both dry and wet AMD, early identification and treatment may help to prevent permanent effects on vision. Treatments for wet AMD are aimed at the abnormal retinal vascular growth (choroidal neovascularization) associated with this condition and responsible for vision loss. Currently, the most common therapy for wet AMD is intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors. Intravitreal medications approved by the U.S. Food and Drug Administration (FDA) for wet AMD are ranibizumab, pegaptanib, aflibercept, and brolucizumab-dbl. In addition, bevacizumab is a VEGF inhibitor approved for treatment of colorectal and other cancers that is used off-label for treatment of wet AMD. Laser photocoagulation, an older treatment for wet AMD, is no longer

commonly used because it causes blind spots due to retinal damage in areas of treatment.⁵² Photodynamic therapy with administration of verteporfin, a photoreactive agent, followed by exposure of the eye to a low-level, non-thermal photo-activating laser light, is associated with less retinal scarring compared with laser photocoagulation and is an option for subfoveal neovascularization, but associated with high rates of recurrence, and is not a first-line therapy for most patients with AMD.

Current Clinical Practice/Recommendations of Other Groups

The clinical standard for identifying presence of impaired visual acuity is by evaluation of distance visual acuity using the Snellen or ETDRS eye chart or another standardized test of visual acuity. Pinhole visual acuity testing can be used to estimate whether impaired visual acuity is due to correctable refractive error (i.e., vision corrects or improves upon pinhole testing).⁵⁹ Reading distance testing can also be assessed using a handheld card or other screening tool.

Clinically significant cataracts can be visualized on physical examination as change of color or opacities in the lens. Impaired visual acuity due to cataracts should not completely correct with pinhole testing, though partial correction may occur due to decreased light scattering, particularly if myopia related to the cataract is present.⁶⁰

The Amsler grid consists of evenly spaced horizontal and vertical lines (making squares) on a sheet.⁶¹ It is used to detect retinal defects affecting central vision, including AMD, which can be associated with distortion in the boxes on the grid or blank areas in the grid (scotomas). The Amsler grid can also be used by patients as a self-monitoring tool for early signs or progression of macular disease.^{62,63}

Screening questions may be used to elicit self-perceived problems with vision.⁶⁴ Funduscopy examination can also be performed in order to detect asymptomatic or early AMD or other retinal disease. The frequency with which nonstandard visual acuity tests, the Amsler grid, vision screening questionnaires, or funduscopy examination is used in primary care is not known.⁶⁵ Older adults with impaired visual acuity are typically referred to an optometrist or ophthalmologist for further evaluation, correction of refractive error, and other treatments. In a study estimating the level of self-reported access to eye care services, approximately half of U.S. adults older than age 65 years reported receiving an eye examination within the last 12 months.⁶⁶

The American Optometric Association recommends an annual comprehensive eye and vision examination for all adults older than age 65 years, and the American Academy of Ophthalmology recommends a comprehensive examination conducted by an ophthalmologist every 1 to 2 years in patients age 65 years or older (**Table 2**).^{67,68} The American Academy of Family Physicians' recommendation on screening for visual acuity in older adults is in agreement with the USPSTF recommendation (insufficient evidence).⁶⁹

Chapter 2. Methods

Key Questions and Analytic Framework

The scope and key questions (KQs) were developed by the Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers using the methods developed by the USPSTF.⁷⁰ The analytic framework and KQs that guided the review are shown in **Figure 1**. Seven KQs were developed for this review:

Key Questions:

1. What are the effects of vision screening in asymptomatic older adults versus no screening on visual acuity, morbidity or mortality, general or vision-related quality of life, functional status, or cognition?
2. What are the harms of vision screening in asymptomatic older adults versus no screening?
3. What is the diagnostic accuracy of screening for impaired visual acuity due to uncorrected refractive error, cataracts, or AMD?
4. What is the accuracy of instruments for identifying patients at higher risk of impaired visual acuity due to uncorrected refractive error, cataracts, or AMD?
5. What are the effects of treatment for wet or dry AMD versus placebo or no treatment on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?
6. What are the effects of newer (aflibercept or brolocizumab-dbl) versus older VEGF inhibitors for wet AMD on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?
7. What are the harms of treatment for early impaired visual acuity due to wet or dry AMD?

Search Strategies

A research librarian searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, and Ovid MEDLINE (January 2015 to February 9, 2021) for relevant studies and systematic reviews. The search relied primarily on the previous systematic review for the USPSTF to identify potentially relevant studies published before 2015 (we reassessed all articles included in that systematic review using the eligibility criteria). Search strategies are available in **Appendix A1**. To supplement electronic searches, we reviewed reference lists of relevant articles.

Study Selection

At least two reviewers independently evaluated each study to determine eligibility. We selected

studies on the basis of inclusion and exclusion criteria developed for each KQ (**Appendix A2**).

This systematic review carries forward prior questions (from the 2016 review for the USPSTF) on the benefits and harms of screening versus no screening, and diagnostic accuracy of screening. The population of interest was older adults, defined as those 65 years of age or older. Screening tests include tests of vision conducted in primary settings as well as questionnaires related to problems with vision. Multi-component screening studies were excluded if the vision component was not evaluated separately or if the intervention was not feasible to conduct in a primary care setting (e.g., required eye specialty training or equipment). Because evidence on the benefits and harms of treatment for cataracts and refractive error are well-established and unlikely to have changed, we focused on benefits and harms of treatment for wet and dry AMD. For wet AMD, we focused on intravitreal injection of VEGF inhibitors, which are considered first-line therapy and the most commonly used treatment in clinical practice. Because newer VEGF inhibitors approved by the FDA (aflibercept and brolocizumab-dbl) have not been evaluated in placebo-controlled trials, a new KQ on the benefits and harms of these medications versus other VEGF inhibitors was added. Second-line therapies for wet AMD such as laser photocoagulation and PDT with verteporfin were not eligible. For dry AMD, we focused on the effectiveness of vitamins and antioxidants. Like the prior review for the USPSTF, this review did not address treatments for prevention of impaired visual acuity. An updated version⁷¹ of a systematic review⁷² on treatment for dry AMD that was utilized in the prior USPSTF review was included. Otherwise this report utilized primary studies; systematic reviews were used to identify potentially eligible studies for inclusion. In accordance with USPSTF methods, studies rated poor quality (see below) were excluded.

The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists the included studies, and **Appendix A5** lists the excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

For studies meeting inclusion criteria, we created data abstraction forms to summarize characteristics of study populations, interventions, comparators, outcomes, study designs, settings, and methods. One investigator conducted data abstraction, which was reviewed for completeness and accuracy by another team member.

Predefined criteria were used to assess the quality of individual controlled trials, systematic reviews, and observational studies by using criteria developed by the USPSTF; studies were rated as “good,” “fair,” or “poor” per USPSTF criteria, depending on the seriousness of the methodological shortcomings (**Appendix A6**).⁷⁰ For each study, quality assessment was performed by two team members. Disagreements were resolved by consensus.

Data Synthesis and Analysis

A random effects meta-analysis conducted for the prior USPTF review on the effects of VEGF

inhibitors versus sham on visual acuity outcomes (the likelihood of visual acuity gain, visual acuity loss, or having vision 20/200 or better) was carried forward for this review; there were no new trials of VEGF inhibitors versus sham. The meta-analysis calculated pooled risk ratios (RRs) and absolute risk differences using Review Manager 5.2 (Nordic Cochrane Centre) and stratified by the VEGF inhibitor used. Results were considered statistically significant if the *P* value was less than 0.05 based on 2-sided testing, and statistical heterogeneity was measured using the *I*². No new evidence suitable for meta-analysis was identified for this review, due to small numbers of studies and heterogeneity in populations, interventions, and outcomes.

For all Key Questions, the overall strength of evidence was determined using the approach described in the USPSTF Procedure Manual.⁷⁰ The strength of evidence was rated “high”, “moderate”, “low” or “insufficient” based on study quality, consistency of results between studies, precision of estimates, study limitations, and risk of reporting bias.⁷⁰ Additionally, the applicability of the findings to U.S. primary care populations and settings was assessed. Discrepancies were resolved through consensus discussion.

USPSTF Involvement

This review was funded by AHRQ. AHRQ staff and USPSTF members participated in developing the scope of the work and reviewed draft reports, but the authors are solely responsible for the content.

Expert Review and Public Comment

The draft research plan was posted for public comment from February 13, 2020 to March 11, 2020. The comments were reviewed and no changes to the scope or Key Questions were required. A final research plan was posted on the USPSTF’s Web site on June 11, 2020.

A draft version of this report has been reviewed by content experts and representatives of Federal partners (**Appendix A7**), USPSTF members, and AHRQ Medical Officers, and minor edits were made for clarity. The draft will be posted for public comment prior to finalization.

Chapter 3. Results

A total of 5,170 new references from electronic database searches and manual searches of recently published studies were reviewed and 339 full-text papers were evaluated for inclusion. A total of 25 studies were included in this review (13 trials, 11 diagnostic accuracy studies, and one systematic review [of 19 trials]) in 50 publications. Sixteen studies were carried forward from the 2016 review for the USPSTF, eight studies were new, and the systematic review⁷² utilized in the 2016 review for the USPSTF was updated⁷¹ to include six new trials. Included studies and quality ratings are described in **Appendix B**.

Key Question 1. What are the effects of vision screening in asymptomatic older adults versus no screening on visual acuity, morbidity or mortality, general or vision-related quality of life, functional status, or cognition?

Summary

- Four randomized trials (N=4,819) found no difference between vision screening in primary care-applicable settings versus no screening, usual care, or delayed screening on vision and other clinical outcomes in older adults; 1 small trial (n=188) was not included in the 2016 USPSTF review.

Evidence

The prior USPSTF review^{1,2} included three fair-quality cluster-randomized trials⁷³⁻⁷⁵ (sample sizes 261 to 3,249, N=4,631) of vision screening in older adults in primary care-applicable settings. None of the trials found beneficial effects of screening on visual acuity, likelihood of vision disorders, or functional impairment related to vision with vision screening. For this update, all three trials were carried forward, and one additional randomized controlled trial (RCT) (n=188) was added^{76,77} (**Table 3, Appendix B Table 1**).

The trials from the prior report compared universal versus targeted vision screening,⁷⁵ immediate versus delayed vision screening,⁷³ and vision screening versus usual care;⁷⁴ the additional trial compared vision screening versus no screening.⁷⁶ In all trials, vision screening was part of a larger, multicomponent health screen for older adults including other assessments (e.g., hearing, mobility, cognition); however, effects of vision screening versus no screening were evaluated separately. Screening methods varied: a brief screening questionnaire plus the Glasgow visual acuity chart followed by pinhole testing for persons with visual acuity worse than 6/18 (20/60),⁷⁵ assessment of difficulty in recognizing a face and/or reading normal letters in a newspaper, along with Snellen visual acuity eye chart,^{73,78} a screening question and clinical summary followed by the Snellen eye chart,⁷⁴ and an ETDRS visual acuity chart, measurement of binocular near vision and visual field testing, along with screening questions.⁷⁶ The previously included trials were conducted in community or general practice settings and screening was conducted by general

practitioners, office staff, or trained nurses. The additional trial⁷⁶ was conducted in a geriatric day hospital, though screening could be done via home visit if needed. Screening was conducted by study investigators (geriatric medicine or eye specialist) or an orthoptist, but the study was considered primary care-applicable because the screening methods consisted of visual acuity testing, binocular near vision, and visual field confrontation testing.

Across all four studies, one trial each was conducted in the U.S., the United Kingdom (U.K.), the Netherlands, and Australia; race and ethnicity were not reported. Mean ages ranged from 76 to 83 years and the proportion female ranged from 34 to 62. The duration of followup ranged from 6 months to 5 years. All trials were rated fair-quality (**Appendix B Table 2**). Methodological limitations included unclear allocation concealment and blinding methods, and high loss to followup.

None of the previously included trials found any beneficial effects of screening on visual acuity, likelihood of vision disorders, or vision-related functional impairment. In the largest (n=3,249) trial, universal vision screening identified about 10 times as many patients with impaired visual acuity and correctable impairment compared with targeted screening, but there was no difference in the likelihood of visual acuity worse than 20/60 at 3- to 5-year followup (relative risk [RR], 1.07 [95% confidence interval [CI], 0.84 to 1.36]).⁷⁵ There were also no differences in vision-related quality of life (National Eye Institute – Visual Function Questionnaire [NEI-VFQ] mean difference 0.4 [95% CI -1.7 to 2.5] on a 0 to 100 scale). Another trial (n=1,121) found no differences between immediate versus delayed in likelihood of visual disorders in the 2nd year of followup (51% [95% CI 45% to 58%] vs. 47% [95% CI 42% to 52%]; p=0.68).^{73,78} The third trial found no difference between screening versus usual care in likelihood of improvement in vision at 6 months (20% [20/99] vs. 24% [31/131], RR 0.85 [95% CI 0.52 to 1.40]).⁷⁴ The fourth, small trial (n=188), which was not in the prior USPSTF review, found no statistically significant differences between screening versus no screening in mean visual acuity (39 letters vs. 35 letters, p=0.25) or bilateral visual impairment (35% vs. 47%, p=0.17) at 1 year.⁷⁶

In the largest trial, only half of the patients advised to see an eye care provider after vision screening actually received new glasses, which could have attenuated potential benefits.⁷⁵ Other reasons for lack of benefit in the screening trials may include attrition (24% to nearly 60% in the larger trials at 2 to 5 years of followup),^{73,75,78} similar frequency of vision disorder detection and treatment in the screening and control groups in one trial,⁷⁴ use of a screening question to identify persons for further testing in one trial,⁷⁴ low uptake of recommended interventions in one trial,⁷³ or high rates of antecedent eye professional care in screened and unscreened groups.⁷⁶

Key Question 2. What are the harms of vision screening in asymptomatic older adults versus no screening?

Summary

- No trial of screening versus no screening, usual care, or delayed screening (including one fair quality trial added for this update) reported harms.

Evidence

None of the three fair-quality cluster-randomized trials included in the prior USPSTF review of vision screening in primary care-applicable settings versus no screening, usual care, or delayed screening reported harms.⁷³⁻⁷⁵ One additional fair-quality trial added for this update (described above) also did not report harms.⁷⁶

Key Question 3. What is the diagnostic accuracy of screening for impaired visual acuity due to uncorrected refractive error, cataracts, or AMD?

Summary

- Three studies (N=6,493) in the prior USPSTF review found no visual acuity test associated with both high sensitivity and specificity for identifying visual conditions compared with a complete examination by an ophthalmologist. Based on a visual acuity threshold of <20/30 or <20/40, sensitivity ranged from 0.27 to 0.75 and specificity from 0.51 to 0.87, with positive likelihood ratios of 1.54 to 5.69 and negative likelihood ratios of 0.30 to 0.84.
- Two studies (N=380) in the prior USPSTF review on development and refinement of a computerized vision screening tool with four tests of vision function found optimal accuracy with high contrast visual acuity (threshold <20/30), which was associated with sensitivity of 0.77 (95% CI 0.69 to 0.84) and specificity of 0.73 (95% CI 0.62 to 0.82) for identification of significant acuity-impairing eye conditions.
- One study (n=371) in the prior USPSTF review found a cutoff score of the Minimum Data Set Vision Patterns section (score ≥ 1 on a 0 to 4 scale) associated with sensitivity of 0.52 (95% CI 0.45 to 0.59) and 0.75 (95% CI 0.68 to 0.82) for detecting visual acuity $\leq 20/40$, for a positive likelihood ratio of 2.11 (95% CI 1.56 to 2.86) and negative likelihood ratio of 0.64 (95% CI 0.54 to 0.75).
- One study (n=50) in the prior USPSTF review found that 100 percent of cataract patients and 80 percent of AMD patients were correctly identified by a geriatrician compared to an ophthalmologist, with no false positives.
- One new, fair-quality study (n=104) found visual acuity mobile application screening associated with sensitivity of 0.98 (95% CI 0.91 to 1.00) and specificity 0.94 (95% CI 0.82 to 0.99) for identifying visual acuity $\leq 20/40$ versus the standard ETDRS chart, for a positive likelihood ratio of 15.07 (95% CI 5.04 to 45.03) and negative likelihood ratio of 0.02 (95% CI 0.00 to 0.13).

Evidence

We included eight studies on the accuracy of screening tests for impaired visual acuity due to visual conditions such as cataracts, refractive error, and AMD in older adults (**Appendix B Tables 3-4**). Of these, the prior USPSTF review² included seven studies (reported in six publications)⁷⁹⁻⁸⁴ and one study⁸⁵ was new for this review. One additional study from the prior

USPSTF report was excluded due to poor quality (only 56 percent of those screened received the reference standard).⁸⁶

In the studies carried forward from the prior USPSTF review, screening was conducted using an eye chart (Snellen or logMAR, 3 studies),^{79,80,84} a computerized tool based on four tests of vision function (2 studies),⁸¹ score on the Minimum Data Set (MDS) Vision Patterns section (1 study),⁸³ geriatrician examination (1 study),⁸² and the Amsler grid (1 study).⁷⁹ The reference standard was a complete examination by an ophthalmologist in all studies, except for the study that evaluated the MDS Vision Patterns section.⁸³ In that study, the reference standard was visual acuity evaluation using a chart. Two studies,^{80,84} one of which was part of the Blue Mountains Eye Study,⁸⁰ included 3,654 and 2,522 participants. In the other studies, sample sizes ranged from 50 to 371 (total N=7,294). Studies were conducted in the U.S., Australia, and the U.K. Settings included primary care clinics, general eye clinics, hospitals, community day centers, and nursing homes. Screening was performed by primary care physicians, general practitioners, geriatricians, or trained research staff; in two studies the screener was unclear.^{79,80} The mean age of participants ranged from 77 to 81 years or enrolled persons older than 49, 50, or 64 years of age, with the exception of one study in which 21 percent of the population was at least 60 years of age (mean age 44 years).⁷⁹ The proportion female was 54 to 81 percent in studies that reported this information. Two studies reported race/ethnicity; in one study, the majority (77%) of participants were Latino,⁷⁹ in the other the proportion White was 73 percent and the proportion Black 26 percent.⁸³ Refractive error was present in 5 to 58 percent of participants, cataracts in 17 to 70 percent, and AMD in 4 to 29 percent. Impaired visual acuity at baseline was reported in one study at 41 percent.⁸³

One new study (n=104) conducted in the U.S. compared visual acuity screening using a mobile iPod application against the standard ETDRS chart⁸⁵ (**Appendix B Tables 3-4**). Mean age was 67 years. The proportion female was 63 percent, the proportion White was 69 percent and the proportion Black was 25 percent. The proportion of patients with visual acuity $\geq 20/40$ was 44 percent.

All studies were rated as fair-quality (**Appendix B Table 5**). Methodological shortcomings included unclear interpretation of the reference standard independently from the screening test, unclear methods for selecting patients for inclusion, and failure to apply the reference standard to all patients. Four studies did not pre-specify thresholds used to define an abnormal screening test,^{79-81,85} including two studies^{81,85} that reported on the development of a screening tool.

Three studies (N=6,493) reported diagnostic accuracy of visual acuity testing with a chart compared to a complete examination by an ophthalmologist (**Appendix B Tables 3-4**).^{79,80,84} One large study (n=2,522) found presenting distance visual acuity $\leq 20/30$ associated with sensitivity of 0.74 (95% CI 0.72 to 0.76) and specificity of 0.87 (95% CI 0.84 to 0.89) for any ocular disease excluding refractive error, for a positive likelihood ratio of 5.69 and negative likelihood ratio of 0.30.⁸⁴ Sensitivity was similar (0.77, 95% CI 0.75 to 0.79) but specificity lower (0.68, 95% CI 0.65 to 0.71) when screening was based on near visual acuity at the same visual acuity threshold. However, another large study (n=3,654) found distance visual acuity $\leq 20/30$ associated with lower sensitivity of 0.47 (95% CI, 0.44 to 0.50) for any eye disease,

with specificity of 0.74 (95% CI, 0.72 to 0.76), for a positive likelihood ratio of 1.81 (95% CI, 1.65 to 1.98) and negative likelihood ratio of 0.72 (95% CI, 0.68 to 0.76).⁸⁰ Accuracy was similar for identification of persons with specific conditions (cataracts or early AMD). Use of alternate screening thresholds ($\leq 20/40$ or $\leq 20/60$) or screening based on near distance, pinhole, or reading acuity also was not associated with both high sensitivity and specificity (**Appendix B Tables 3-4**). A third, smaller study (n=317) also reported suboptimal sensitivity of visual acuity screening.⁷⁹ It found distance visual acuity $\leq 20/30$ associated with sensitivity of 0.75 (95% CI, 0.69 to 0.81) and specificity of 0.51 (95% CI, 0.42 to 0.61) for any ocular disease excluding refractive error, for a positive likelihood ratio of 1.54 (95% CI, 1.26 to 1.90) and negative likelihood ratio of 0.48 (95% CI, 0.36 to 0.65). Higher screening thresholds ($\leq 20/40$ or $\leq 20/60$) were associated with lower sensitivity but higher specificity; results were similar for screening based on near distance visual acuity. In the latter two studies, discrimination based on the area under the receiver operating characteristic curve (AUC) for various measures of visual acuity ranged from 0.72 and 0.83;^{79,80} the AUC was not reported in the other study.⁸⁴ A challenge in interpreting data on diagnostic accuracy of screening is the uncertain clinical significance of visual conditions identified on full ophthalmological examination but not associated with reduced visual acuity.

Two studies (reported in one publication) evaluated a computerized vision screening tool (Computer Vision Screener).⁸¹ The studies (n=180 and n=200) were conducted in the U.K. in participants 65 years or older (mean age, 77 years). Of these, about 30 percent had cataracts, 30 to 39 percent had significant refractive error, and 22 to 29 percent had significant macular degeneration; 51 to 58 percent were classified as having correctable visual loss. The reference standard was a “gold standard eye exam” that included detailed history and symptoms, slit lamp and dilated fundusoscopic examination, tests of visual acuity, visual field, orthoptic tests, and others. The original version of the screening tool included questions on history and symptoms as well as six tests of vision function (near visual acuity, visual field, fixation disparity, stereoacuity, high contrast distance visual acuity, and low contrast distance visual acuity). The first study reported initial development and testing of the computerized vision screening tool, to inform further refinement. For high-contrast or low-contrast visual acuity, sensitivity for identifying persons with significant acuity-impairing eye conditions (correctable visual loss from cataracts or refractive error or AMD at risk of progression) ranged from 0.67 to 0.86 and specificity ranged from 0.50 to 0.60. Due to poor performance, two items (fixation disparity and stereoacuity) were dropped from the tool. In the second study, which evaluated the modified computerized vision screening tool with four items, optimal accuracy for identifying persons with significant acuity-impairing eye conditions was observed with high contrast visual acuity (threshold >0.19 logMAR [20/30]), which had a sensitivity of 0.77, 95% CI 0.69 to 0.84), specificity of 0.73 (95% CI 0.62 to 0.82), positive likelihood ratio of 2.85 and negative likelihood ratio of 0.32. Results were similar for the combination of abnormal high contrast visual acuity (threshold >0.19 logMAR [20/30]) or near visual acuity (threshold unclear). With this combination, sensitivity was 0.80 (95% CI, 0.72 to 0.86) and specificity 0.68 (95% CI, 0.57 to 0.77).

Another study (n=371) compared the scores on the MDS Patterns section against a standard visual acuity (ETDRS chart) test for detecting impaired visual acuity.⁸³ Participants age 55 years or older (mean age, 81 years) were recruited from nursing homes and assessed by

trained research staff (not further described). The prevalence of impaired visual acuity was about 40 percent. The MDS Visual Patterns section is scored from 0 to 4, with 0 indicating adequate vision and 4 severely impaired vision. Diagnostic accuracy was poor using any cutoff score on the MDS Visual Patterns. Using a cutoff score of 1 or greater (0 indicating adequate vision and scores of 1 to 3 indicating various degrees of impairment), sensitivity of the MDS Visual Patterns section for detecting distance visual acuity worse than 20/40 was 0.52 (95% CI 0.45 to 0.59) and specificity was 0.75 (95% CI 0.68 to 0.82), resulting in a positive likelihood ratio of 2.11 (95% CI 1.56 to 2.86) and a negative likelihood ratio of 0.64 (95% CI 0.54 to 0.75).

One study (n=104) developed and tested visual acuity screening with a mobile (iPod) ETDRS application against the standard (chart) ETDRS.⁸⁵ The mobile application utilized randomized ETDRS letters at the Snellen equivalent of 20/40 and 20/200 visual acuity. Patients were selected from tertiary referral glaucoma and retina practices in the U.S. Mean age was 67 years and 63 percent were female. For visual acuity \leq 20/40, incorrect identification of four visual acuity <20/40 images was associated with sensitivity of 0.98 (95% CI 0.91 to 1.00) and specificity of 0.94 (95% CI, 0.82 to 0.99), for a positive likelihood ratio of 15.07 (95% CI, 5.04 to 45.03) and negative likelihood ratio of 0.02 (95% CI, 0.00 to 0.13). For visual acuity <20/200, incorrect identification of four <20/200 images was associated with sensitivity of 0.92 (95% CI, 0.64 to 1.00), specificity of 0.92 (95% CI, 0.85 to 0.97), positive likelihood ratio of 12.00 (95% CI, 5.79 to 24.87) and NLR 0.08 (95% CI, 0.01 to 0.55).

One study (n=317) found the Amsler grid associated with poor accuracy for identifying any ocular disease excluding refractive error (sensitivity 0.20, 95% CI, 0.14 to 0.27, specificity 0.88, 95% CI, 0.80 to 0.94, positive likelihood ratio 1.65, 95% CI, 0.90 to 3.06, and negative likelihood ratio 0.91, 95% CI, 0.82 to 1.01) (**Appendix B Tables 3-4**).⁷⁹ Another study in the prior USPSTF review (n=50) compared the accuracy of an examination by a geriatrician compared with an ophthalmologist for identifying persons with previously undiagnosed cataracts or AMD (**Appendix B Tables 3-4**).⁸² All patients were 64 years of age or older. The proportion of patients with cataracts was 18 percent and the proportion with previously undiagnosed AMD was 8 percent. The study found that 100 percent of cataract patients and 80 percent of AMD patients were correctly identified by a geriatrician, with no false-positives.

Key Question 4. What is the accuracy of instruments for identifying patients at higher risk of impaired visual acuity due to uncorrected refractive error, cataracts, or AMD?

Summary

- Two studies (n=1,121 and 3,997) included in the prior USPSTF review and one new study (n=85) found that screening questions were not accurate (associated with both high sensitivity and specificity) for identifying older persons with impaired visual acuity compared with the Snellen or low vision eye chart. Sensitivities ranged from 0.17 to 0.81 and specificities from 0.19 to 0.84, resulting in positive likelihood ratios of 0.26 to 2.69

and negative likelihood ratios of 0.41 to 3.23

Evidence

We included three studies on the diagnostic accuracy of screening questions for identifying older adults with decreased visual acuity. Of these, two studies^{73,78,87} were included in the 2016 USPSTF review and one study⁸⁸ was new for this review. Two other studies in the prior USPSTF report were excluded due to poor quality (insufficient reporting of methods and results or high proportion of patients did not undergo the reference standard).^{86,89}

The sample sizes of the studies carried forward from the prior USPSTF report were 1,121 and 3,997. The mean age was 81 years in one study,^{73,78} in the other study⁸⁷ 37 percent of patients were 65 to 74 years of age and the remainder were <65 years old. One study⁸⁷ conducted in the U.S. reported that 61 percent of participants were female and 79 percent were White. In the other study, conducted in the Netherlands, sex and race/ethnicity were not reported.^{73,78} The studies evaluated single screening questions against the reference standard Snellen chart (**Appendix B Table 6**). Screening was performed by general practitioners in one study^{73,78} and by study personnel in mobile examination units in the other.⁸⁷ Both studies were rated fair-quality (**Appendix B Table 7**). Methodological limitations included unclear interpretation of the reference standard from the screening test, and vice versa. One study did not include all patients in the analysis.

Both studies reported poor accuracy of screening questions for identifying persons with decreased visual acuity (**Appendix B Table 8**). One study found a question on trouble recognizing faces associated with sensitivity of 0.40, 95% CI, 0.31 to 0.49 and specificity of 0.19, 95% CI, 0.16 to 0.21 for visual acuity ≤ 0.3 (~20/60) on the Snellen.^{73,78} The prevalence of Snellen visual acuity < 0.3 was 11 percent. A question on trouble reading the newspaper was associated with a sensitivity of 0.17, 95% CI, 0.12 to 0.25 and specificity of 0.33, 95% CI, 0.30 to 0.36 for identifying persons with difficulty with low vision chart at reading distance, for a positive likelihood ratio of 0.26, 95% CI, 0.18 to 0.37 and negative likelihood ratio of 2.47, 95% CI, 2.20 to 2.78. In the other study, a question on trouble seeing was associated with sensitivity of 0.34, 95% CI, 0.28 to 0.41 and specificity of 0.84, 95% CI, 0.82 to 0.86 for identifying persons with visual acuity $\leq 20/50$ on the Snellen,⁸⁷ for a positive likelihood ratio of 2.15, 95% CI, 1.72 to 2.69 and negative likelihood ratio of 0.78, 95% CI, 0.71 to 0.86. Approximately 2/3 of patients had visual acuity $\leq 20/25$. Results were similar for identifying persons with visual acuity $\leq 20/100$.

A new, fair-quality study (**Appendix B Tables 6-8**) was smaller (n=85). It assessed a screening question in patients 69 years of age or older in Switzerland.⁸⁸ About half of patients were female. The study found a question by family physicians or internists on trouble reading the newspaper associated with sensitivity of 0.81, 95% CI, 0.69 to 0.90 and specificity of 0.46, 95% CI, 0.26 to 0.67 for identification of persons with any visual impairment (not defined) based on a comprehensive geriatric assessment that included visual acuity (Snellen) and visual field testing. The positive likelihood ratio was 1.5, 95% CI, 1.0 to 2.2 and negative likelihood ratio was 0.4, 95% CI, 0.2 to 0.8.

Key Question 5. What are the effects of treatment for wet or dry AMD versus placebo or no treatment on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?

Summary

VEGF Inhibitors for Wet AMD

- No new trials compared intravitreal injection with VEGF inhibitors versus sham injection.
- In four randomized trials (N=2,086) included in the prior USPSTF review, intravitreal injection with VEGF inhibitors was associated with greater likelihood of ≥ 15 letters of visual acuity gain (RR, 2.92, 95% CI, 1.20 to 7.12, $I^2=76\%$; absolute risk difference [ARD] 10%), < 15 letters of visual acuity loss (RR, 1.46, 95% CI, 1.22 to 1.75, $I^2=80\%$; ARD 27%), and having vision 20/200 or better (RR, 1.47, 95% CI, 1.30 to 1.66, $I^2=42\%$; ARD 24%) at 1 year versus sham injection.
- Based on one trial included in the prior USPSTF review, VEGF inhibitors were associated with better vision-related function and quality of life measures versus sham injection at 1 and 2 years, the difference (~ 8 points on a 0 to 100 scale) was above the threshold for a clinically important difference (4 to 6 points).

Antioxidant Vitamins and Minerals for Dry AMD

- The large (n=3,640), good-quality Age-Related Eye Disease Study (AREDS), which was included in prior USPSTF reviews, remains the most important trial for informing treatment for dry AMD. At 6.3 years, the combination of antioxidants plus zinc was associated with decreased risk of progression to advanced AMD versus placebo (odds ratio [OR], 0.72, 99% CI, 0.52 to 0.98).⁹⁰ In persons with more advanced (category 3 or 4) AMD, antioxidants plus zinc were associated with decreased risk of visual acuity loss ≥ 15 lines on the ETDRS (OR, 0.73, 99% CI, 0.54 to 0.99). Ten-year followup results were consistent with the 6.3 year results.
- An updated (2017) Cochrane systematic review included 19 trials (13 trials in the 2012 Cochrane review used in the prior USPSTF review) of antioxidant multivitamins, zinc, lutein and zeaxanthin, or vitamin E for dry AMD; results were heavily influenced by AREDS.
 - Antioxidant multivitamins were associated with decreased risk of progression to late AMD (3 trials, N=2,445 people, OR 0.72, 95% CI 0.58 to 0.90; 73% of patients from AREDS) and ≥ 3 lines visual acuity loss (1 trial [AREDS], N=1,791 people, OR 0.77, 95% CI 0.62 to 0.96) versus placebo.
 - Zinc was associated with decreased risk of progression to late AMD versus placebo (3 trials, N=3,790 people, OR 0.83, 95% CI 0.70 to 0.98; 96% of patients from AREDS) and decreased risk of ≥ 3 visual acuity loss lines that was of

borderline statistical significance (2 trials, 3,791 people, RR 0.87, 95% CI 0.75 to 1.00; 96% of patients from AREDS).

- Lutein and zeaxanthin or vitamin E were associated with little or no effect on risk of AMD progression.
- Evidence on the effects of other vitamins and mineral treatments remains limited, with no clear effects on AMD progression or visual acuity.

Evidence

VEGF Inhibitors for Wet AMD

No new trials of intravitreal injection with VEGF inhibitors versus sham injection were identified. The prior USPSTF review included four RCTs (reported in five publications) of intravitreal injection with VEGF inhibitors versus sham injection, all of which were carried forward.⁹¹⁻⁹⁵ The trials were the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) trial,^{91,92,95} the two VEGF Inhibition Study in Ocular Neovascularization (VISION) trials (reported in one publication),⁹³ and the Phase IIIB, multicenter, randomized double-masked sham Injection-controlled study of the Efficacy and safety of Ranibizumab (PIER) trial.⁹⁴

Sample sizes ranged from 184 to 1,208 participants (N=2,086); 54 to 68 percent of participants were female (**Appendix B Table 9**). Mean age was 77 to 78 years in MARINA and PIER; in the VISION trials,⁹³ 61 percent of the population was older than age 75 years. Studies were conducted in the U.S in two trials, and the other trials had various countries (U.S., Canada, Europe, Israel, Australia, and South America). Mean baseline visual acuity was about 20/80 in three studies; in the fourth study (PIER),⁹⁴ 69 percent of the population had baseline visual acuity between 20/40 and 20/200. The MARINA⁹⁵ and PIER⁹⁴ trials evaluated ranibizumab 0.3 to 0.5 mg every 1 to 3 months and the VISION⁹³ trials evaluated pegaptanib (0.3 to 3.0 mg) every 6 weeks. The proportion of patients with lesions classified as occult choroidal neovascularization ranged from 38 to 63 percent; the proportion classified as minimally classic ranged from 36 to 38 percent; and the proportion with predominantly classic ranged from 19 to 26 percent. The duration of followup ranged from 1 year to 2 years. All trials were appropriately randomized, used a blinded design, and had low attrition, and were rated good-quality (**Appendix B Table 10**).

AMD Progression and Changes in Visual Acuity

Pooling data from all four trials (N=2,086), VEGF inhibitor treatment was associated with greater likelihood of ≥ 15 ETDRS letters of visual acuity gain (RR, 2.92, 95% CI, 1.20 to 7.12, $I^2=76\%$; ARD, 10%, 95% CI, -7% to 27%) (**Figure 2**) and < 15 letters of visual acuity loss (RR, 1.46, 95% CI, 1.22 to 1.75, $I^2=80\%$; ARD, 27%, 95% CI, 12% to 42%) (**Figure 3**) versus sham injection at 1 year.⁹³⁻⁹⁵ Although statistical heterogeneity was high, estimates from all trials favored VEGF inhibitors and results were similar when results were stratified by VEGF inhibitor. For visual acuity gain ≥ 15 letters, estimates were similar for ranibizumab (2 trials, RR 2.86, 95% CI 0.64 to 12.73) and pegaptanib (2 VISION trials, RR 2.83, 95% CI 1.23 to 6.52). For visual acuity loss < 15 letters, estimates were also similar for ranibizumab (RR 1.56, 95% CI

1.40 to 1.74) and pegaptanib (RR 1.24, 95% CI 1.11 to 1.39). Use of VEGF inhibitors was also associated with greater likelihood of vision 20/200 or better at 1 year versus sham injection, with less statistical heterogeneity (RR 1.47, 95% CI 1.30 to 1.66, $I^2=42%$; ARD, 24%, 95% CI, 12% to 37%) (**Figure 4**). Only the MARINA trial (n=716) reported effects of VEGF inhibitors versus sham at longer (2-year) followup.⁹⁵ It found ranibizumab associated with greater likelihood of ≥ 15 letters visual acuity gain (RR 7.86, 95% CI 4.08 to 15), < 15 letters of visual acuity loss (RR 1.72, 95% CI 1.52 to 1.94), and having 20/200 vision or better (RR 1.63, 95% CI, 1.44 to 1.86).⁹⁵

In a posthoc analysis of the MARINA trial, beneficial effects of ranibizumab were observed in patients with intact or impaired baseline visual acuity. Among patients (n=473) with baseline visual acuity worse than 20/40 (n=473), ranibizumab was associated with greater likelihood of visual acuity improvement to 20/40 or better at 1 year versus sham (27.9% vs. 10.6%, RR 2.64, 95% CI 1.41 to 4.92) or 2 years (31.9% vs. 7.7%, RR 4.13, 95% CI, 2.03 to 8.42) followup (**Appendix B Table 9**).⁹¹ Ranibizumab was also associated with increased likelihood of maintaining good visual acuity at 2 years among patients (n=243) with baseline visual acuity better than 20/40 (77.2% vs. 56.4%, RR 1.37, 95% CI 1.14 to 1.64).

Vision-Related Function

As described in the prior USPSTF review, ranibizumab was associated with better vision-related function scores at both 1 and 2 year follow-up compared with sham, based on the MARINA trial.⁹² On the composite NEI-VFQ-25 (0 to 100 scale), mean improvement was +5.2 (95% CI 3.5 to 6.9) for ranibizumab 0.3 mg and +5.6 (95% CI 3.9 to 7.4) for ranibizumab 0.5 mg dose versus -2.8 (95% CI -4.6 to -1.1) for sham ($p<0.001$ for sham versus either dose). Findings were similar on NEI-VFQ-25 subscale scores for general vision, mental health, social functioning, and driving (**Appendix B Table 9**). The difference of about 8 points on the NEI-VFQ-25 was above published thresholds for minimum clinically important differences (4 to 6 points on a 0 to 100 scale).⁹⁶

The MARINA trial found ranibizumab 0.3 and 0.5 mg associated with increased likelihood of driving at 24 months versus sham among those who drove at baseline (81% vs. 78% vs. 67%, respectively; $p<0.05$ for either dose versus sham); there was no difference in the proportion of drivers at 24 months among those who were not driving at baseline (9% for 0.5 mg dose vs. 7% for sham; $p=0.65$; **Appendix B Table 9**).⁹¹

Mortality

Trials of VEGF inhibitors were not designed to evaluate mortality and few deaths were reported, resulting in imprecise estimates. As described in the prior USPSTF review, the MARINA trial found no difference between ranibizumab versus sham in all-cause (2% vs. 3%; RR 0.91, 95% CI 0.34 to 2.44) or vascular (1% vs. 2%; RR 0.74, 95% CI 0.21 to 2.60) mortality after 2 years (**Appendix B Table 9**).⁹⁵ The VISION trials reported similar rates of mortality (2%) in treatment and sham groups;⁹³ there were no deaths in the PIER trial.⁹⁴

Antioxidant Vitamins and Minerals for Dry AMD

The prior USPSTF review^{1,2} included the large, good-quality, AREDS trial⁹⁰ (n=3,640) with 10-

year followup,⁹⁷ a good-quality systematic review of 13 trials (N=6,150, including AREDS⁷²), and two additional trials^{98,99} (N=180) not included in the systematic review on antioxidant multivitamins and minerals and other supplements for dry AMD versus placebo. A different Cochrane systematic review¹⁰⁰ and one other trial¹⁰¹ included in the prior USPSTF report were excluded from this update because they addressed ineligible interventions (ginkgo biloba and fish oil).

The AREDS trial remains the most important evidence on treatment for dry AMD (**Appendix B Tables 11-12**). AREDS was a large (n=3,640), good-quality trial conducted in the U.S. of patients with dry AMD and baseline best-corrected visual acuity of 20/32 or better. Patients were randomized to antioxidants (vitamin C 500 mg, vitamin E 400 IU, and beta carotene 15 mg), zinc (zinc oxide 80 mg and cupric oxide 2 mg), antioxidants plus zinc, or placebo. Baseline AMD severity was classified into four categories, ranging from category 1 (no existing AMD and <5 drusen [$<63 \mu\text{m}$] without pigment changes) to category 4 (advanced AMD in one eye with central geographic atrophy or neovascular AMD). The prespecified AMD analysis focused on patients in categories 2 to 4. Among this group, twenty-nine percent were classified as category 2, 44 percent as category 3, and 26 percent as category 4. Nearly half of AREDS participants were age 70 years or older at baseline, 57 percent were women, and 97 percent were White. More than half were either current (8%) or former (49%) smokers. At 6.3 years, the combination of antioxidants plus zinc was associated with decreased risk of progression to advanced AMD (based on receipt of treatment or pre-defined photographic criteria) versus placebo (OR 0.72, 99% CI 0.52 to 0.98).⁹⁰ Estimates for risk of progression to advanced AMD also favored antioxidants alone (OR 0.80, 95% CI, 0.59 to 1.09) and zinc alone (OR, 0.75, 99% CI, 0.55 to 1.03) versus placebo, but differences were not statistically significant. Effects on risk of visual acuity loss ≥ 15 lines on the ETDRS favored antioxidants plus zinc, but the difference was not statistically significant (OR 0.79, 99% CI 0.60 to 1.04) unless the analysis was restricted to persons with category 3 or 4 AMD (OR 0.73, 99% CI 0.54 to 0.99). The prior USPSTF review added ten years results from AREDS,¹⁰² which were consistent with the 6.3 year results. At ten years, the combination of antioxidants plus zinc was associated with decreased risk of progression to advanced AMD (OR 0.69, 99% CI, 0.56 to 0.86) and visual acuity loss ≥ 15 lines (OR 0.76, 99% CI, 0.63 to 0.93) versus placebo.

The prior USPSTF review also included a Cochrane systematic review⁷² of 13 trials of antioxidant multivitamins and mineral supplements for dry AMD. The systematic review findings were heavily influenced by the AREDS trial, which had the longest duration of followup and accounted for most patients in pooled analyses; therefore, conclusions of the systematic review regarding the effectiveness of multivitamins and mineral supplements were similar to AREDS. The systematic review found evidence for vitamins and mineral supplements other than antioxidants and zinc to be too limited to determine effects.

This review includes findings from an updated (2017) version of the Cochrane systematic review⁷¹ with 19 trials^{90,97-99,103-118} (N=11,162) (**Appendix B Tables 13-14**), including AREDS and all trials in the prior USPSTF review, as well as two additional trials not included in the updated Cochrane review^{119,120} (n=80 and 100) (**Appendix B Tables 15-16**). The updated Cochrane systematic review included the large (n=4,203) AREDS 2^{103,121} trial. All patients in AREDS 2 were taking the AREDS formulation or a variation of it (elimination of beta carotene,

lowering of zinc dose, or both). Therefore, although it included a comparison of lutein plus zeaxanthin versus placebo, it may be considered a trial of add-on therapy with lutein plus zeaxanthin rather than a true placebo-controlled trial.

In addition to AREDS 2, the systematic review included two other large trials: AREDS⁹⁷ (n=3,640) and the Vitamin E, Cataract, and Age-related Maculopathy (VECAT) study¹¹⁶ (n=1,193). In the other trials, sample sizes ranged from 14 to 433 (**Appendix B Table 13**). The interventions evaluated were zinc (six trials), lutein (with or without zeaxanthin, five trials), vitamin E (one trial), and various antioxidant multivitamin and mineral combinations (nine trials). Mean age ranged from 66 to 75 years and the percentage of females ranged from 55 to 57, however three other trials recruited mostly males. Studies were conducted in the U.S., Europe, China, and Australia. Race/ethnicity was greater than 80 percent White in the five trials that reported this information. About half of the studies reported best-corrected visual acuity at baseline, which ranged from an average of 78 to 82 letters on the ETDRS chart (approximately 20/25) or 0.05 to 0.45 logMAR (approximately 20/20 to 20/60). Two trials required patients to have visual acuity of 0.20 to 0.40 logMAR (approximately 20/30 to 20/50) for inclusion. The mean duration of followup ranged from 6 months to 6 years, with most <2 years; 6.3 year followup data from AREDS were used. Most studies were assessed as low risk of bias, including the two largest studies, AREDS and VECAT.

The two additional placebo-controlled trials not included in the updated Cochrane review were rated fair-quality (**Appendix B Tables 15-16**).^{119,120} One trial (n=80) evaluated a nutritional supplement containing carotenoids, antioxidants, and omega-3 fatty acids at 2 years,¹¹⁹ and one evaluated α -lipoic acid capsules;¹²⁰ both were compared with placebo. Mean age of participants ranged from 71 to 74 years, and percent female ranged from 44 to 77 percent. The studies were conducted in Italy,¹¹⁹ and China.¹²⁰ At baseline, studies reported best corrected visual acuity of 0.63 logMAR (20/85),¹²⁰ and visual acuity of 48.5 ETDRS letters (approximately 20/100).¹¹⁹ The trials were rated fair-quality.

AMD Progression and Changes in Visual Acuity

The updated (2017) Cochrane systematic review⁷¹ was consistent with the prior (2012) version in finding antioxidant multivitamins and zinc associated with improved outcomes compared with placebo (**Appendix B Table 13**). Results were largely based on the AREDS trials, which accounted for the great majority of patients in pooled analyses and had the longest duration of followup.⁹⁰

Antioxidant vitamins were associated with decreased risk of progression to late AMD versus placebo (3 trials,^{90,105,112} N=2,445 people [73% from AREDS], OR 0.72, 95% CI 0.58 to 0.90; $I^2=0\%$) and decreased risk of progression to ≥ 3 lines visual acuity loss (1 trial,⁹⁰ N=1,791 people, OR 0.77, 95% CI 0.62 to 0.96). There was no difference between antioxidants versus placebo in mean visual acuity (5 trials, N=595, pooled mean difference 0.02 logMAR, 95% CI -0.03 to 0.07; $I^2=38\%$). In AREDS, the risk of progression to advanced AMD at 5 years varied according to baseline severity: 1.3% for category 2, 18% for category 3 (extensive intermediate drusen, large drusen, or noncentral geographic atrophy), and 43% for category 4.⁹⁰ However, results were similar for antioxidant vitamins plus zinc versus placebo when the analysis for progression

to advanced AMD was restricted to category 3 or 4 patients (adjusted OR 0.66, 95% CI 0.47 to 0.93) or when the analysis included categories 2, 3, and 4 (adjusted OR 0.68, 95% CI 0.49 to 0.93).

The review⁷¹ also found zinc associated with decreased risk of progression to late AMD versus placebo (3 trials,^{90,108,115} N=3,790 people [96% from AREDS], OR 0.83, 95% CI 0.70 to 0.98; I²=17.5%). Zinc was associated with decreased risk of ≥ 3 lines visual acuity loss versus placebo but the difference was of borderline statistical significance (2 trials,^{90,111} 3,791 people [96% from AREDS], RR 0.87, 95% CI 0.75 to 1.00; I²=37%).

The review found little or no effect of lutein and zeaxanthin or vitamin E on risk of progression of AMD.⁷¹ Based on the AREDS 2 trial,¹²¹ the addition of lutein plus zeaxanthin to the AREDS formulation was not associated with decreased risk of progression to advanced AMD versus placebo (n=6,891 eyes, RR, 0.92, 98.7% CI, 0.80 to 1.05). AREDS 2 also found no effects of elimination of beta carotene or use of lower-dose zinc and risk of progression to advanced AMD, compared with the AREDS formulation.

Two small (n=80 and 100) fair-quality trials not included in the updated systematic review also evaluated effects of antioxidants versus placebo for dry AMD (**Appendix B Table 15**). One trial¹¹⁹ (n=80) found a combination of carotenoids (lutein 10 mg, astaxanthin 4 mg, zeaxanthin 2 mg), antioxidants (vitamin C 90 mg, vitamin E 30 mg, zinc 22.5 mg plus copper 1 mg), and omega-3 fatty acids (fish oil 500 mg, containing eicosapentaenoic acid [EPA] 185 mg and docosahexaenoic acid [DHA] 140 mg) associated with decreased likelihood of retinopathy worsening (2.1% vs. 15.4%, p=0.05) versus placebo at 2 years, but effects on risk of worsened distance visual acuity (14.6% vs. 19.2%, p=0.74) and near visual acuity (16.7% vs. 34.6%, p=0.08) were not statistically significant. The other trial¹²⁰ (n=100) found no difference in best corrected visual acuity after 3 months between α -lipoic acid 0.2 g/day versus placebo (logMAR 0.66 vs. 0.63, p>0.05); the placebo in this trial was low-dose vitamin C (0.2 g).

Mortality

Trials of antioxidant multivitamins and minerals were not designed to evaluate mortality, though several trials reported this outcome. In AREDS, the largest trial (n=3,640), there was no difference between antioxidant use versus no antioxidant in risk of all-cause mortality (hazard ratio [HR] 1.06, 95% CI 0.93 to 1.21), cardiovascular mortality (RR 1.20, 95% CI, 0.97 to 1.49), cancer mortality (RR 1.07, 95% CI 0.83 to 1.38), or mortality due to other causes (RR 0.94, 95% CI, 0.74 to 1.20) after adjustment for age, sex, race, education, smoking status, body mass index, diabetes, angina, cancer, and hypertension⁹⁷ (**Appendix B Table 11**). However, zinc use was associated with decreased risk of all-cause (adjusted HR 0.83, 95% CI 0.73 to 0.95) and cardiovascular mortality (adjusted RR 0.80, 95% CI, 0.64 to 0.99) versus nonuse, though effects on cancer mortality were not statistically significant (adjusted RR 0.84, 95% CI, 0.65 to 1.08). Two other trials (n=90 and n=1,193) also reported mortality but reported few events and imprecise estimates.^{113,116}

Other Outcomes

Evidence on other outcomes associated with use of antioxidant multivitamins and minerals was limited.

One trial¹¹² (n=110) found multivitamins associated with better vision-related function after 2 years (NEI-VFQ-25, 0-100 scale], mean difference 12.0, 95% CI 4.24 to 20.36). However, three other trials (n=1,193, 108, and 90) found no significant differences between antioxidants or minerals and vision-related function (NEI VFQ- 25 or Visual Function Index [VF-14], also 0-100 scale),^{114,116,122} though reporting of these outcomes was limited. One trial found α -lipoic acid associated with better quality of life (Low Vision Quality of Life instrument, Chinese version, 0 to 125 scale; 82.6 vs. 72.8, $p<0.05$) after 3 months.¹²⁰ Long-term (10-year) followup of AREDS participants found no significant difference in likelihood of cataract surgery in participants taking any active AREDS intervention (antioxidants, zinc, or both) compared with placebo (RR 0.99, 95% CI, 0.89 to 1.10) (**Appendix B Table 11**).¹²³ The AREDS trial also found no differences between antioxidants, zinc, both, or placebo in six cognitive tests after 6.9 years¹²⁴ and the AREDS 2 trial found no difference between lutein/zeaxanthin versus placebo on cognitive function among those on the AREDS formulation.¹²⁵

Key Question 6. What are the effects of newer (aflibercept or brolucizumab-dbl) versus older VEGF inhibitors for wet AMD on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?

Summary

- In three new trials (N=2,738), aflibercept was noninferior to ranibizumab in likelihood of <15 ETDRS letters of visual acuity loss or ≥ 15 letters of visual acuity gain.
- Two new trials (N=2,457) found aflibercept and ranibizumab associated with similar improvements in vision-related function.

Evidence

Two newer VEGF inhibitors (aflibercept or brolucizumab-dbl) have been approved for treatment of wet AMD. Three new trials (reported in four publications) compared aflibercept versus the older VEGF inhibitor ranibizumab.¹²⁶⁻¹²⁹ No trial compared brolucizumab-dbl versus an older VEGF inhibitor. Aflibercept was evaluated in the two similarly designed VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD trials (VIEW1 and VIEW2, reported in one publication)¹²⁷ (n=2,457), and the Comparison of Ranibizumab and Aflibercept for the Development of Geographic Atrophy in Wet AMD Patients (RIVAL)¹²⁶ trial (n=281). Mean ages were 73 and 79 years; 57 and 53 percent of participants were female (**Appendix B Table 9**). One trial was conducted in Australia, and the others had various sites (U.S., Canada, international). Mean baseline visual acuity was ~20/80 in VIEW¹²⁷ and ~20/50 in RIVAL.¹²⁶ In the VIEW trials, the proportion of patients with lesions classified as occult choroidal

neovascularization ranged from 36 to 40 percent; the proportion classified as minimally classic ranged from 32 to 37 percent; and the proportion with predominantly classic ranged from 23 to 29 percent.¹²⁷ In RIVAL, choroidal neovascularization subtypes were 17 percent predominantly classic and 82 percent minimally classic/occult.¹²⁶

The VIEW trials evaluated intravitreal aflibercept injections with initial dosing of 2 mg once monthly, 2 mg every 8 weeks (after 3 initial monthly doses), or 0.5 mg monthly. The RIVAL trial evaluated intravitreal aflibercept 2 mg once monthly. The ranibizumab dose in all trials was 0.5 mg once per month. In the VIEW trial, at week 52 patients were switched to dosing at least every 12 weeks, with the exact frequency depending on disease activity.

The duration of followup ranged from 1 year to 4 years in the VIEW¹²⁷ trials, and 2 years in RIVAL.¹²⁶ All trials were appropriately randomized, used a blinded design, and had low attrition, and were rated good-quality (**Appendix B Table 10**).

AMD Progression and Changes in Visual Acuity

Effects of aflibercept and ranibizumab on visual outcomes were similar. The VIEW trials found intravitreal aflibercept to be noninferior to ranibizumab for likelihood of <15 ETDRS letters of visual acuity loss at 1 year (94.9% vs. 94.3%) (**Appendix B Table 9**).¹²⁷ Aflibercept and ranibizumab were also associated with similar likelihood of ≥ 15 or more letters of visual acuity gain at 1 year (31.4% vs. 32.4%), and likelihood of improvement to 20/40 vision or better (35.2% vs. 35.1%).¹²⁷ In post-hoc analyses of the VIEW trials, effects of aflibercept and ranibizumab were also similar when patients were stratified according to age, baseline visual acuity, baseline lesion size or type of choroidal neovascularization, and baseline central retinal thickness.^{128,129} The RIVAL trial, found aflibercept and ranibizumab to be associated with similar likelihood of <15 letters of visual acuity loss (94% vs. 94%) and ≥ 15 or more letters gain (19% vs. 25%) after 2 years (**Appendix B Table 9**).¹²⁶ Reported mean change in best corrected visual acuity was +6.6 letters (95% CI, 4.7 to 8.5 letters) for the ranibizumab group and +4.6 letters (95% CI, 2.7 to 6.6 letters) for the aflibercept group ($p=0.15$) over 2 years. Mean change in the square root area of macular atrophy was +0.36 mm (95% CI, 0.27 to 0.45 mm) for ranibizumab and +0.28 mm (95% CI, 0.19 to 0.37 mm) for aflibercept, a treatment difference of +0.08 mm [95% CI, -0.05 to 0.21 mm], $p=0.24$) after 2 years. The proportion of patients with macular atrophy increased from 7 to 37 percent for ranibizumab, and from 6 to 32 percent for aflibercept.

Vision-Related Function

In the VIEW trials, aflibercept and ranibizumab were associated with similar improvements from baseline in composite NEI-VFQ-25 scores (**Appendix B Table 9**).¹²⁷ Mean improvements averaged 4.5 to 6.7 points on a 0 to 100 scale.¹²⁷

Mortality

In the VIEW trials, intravitreal aflibercept and ranibizumab were associated with low and similar rates of vascular mortality (0.5% vs. 0.3%, RR 1.47, 95% CI 0.32 to 6.78; **Appendix B Table**

9).¹²⁶ Two year followup from the RIVAL trial reports similar rates of mortality for aflibercept and ranibizumab (4.3% vs. 2.1%, RR 2.02, 95% CI 0.52 to 7.95).¹²⁶

Key Question 7. What are the harms of treatment for early impaired visual acuity due to wet or dry AMD?

Summary

VEGF Inhibitors for Wet AMD

- As described in the prior USPSTF review, four trials reported no differences between VEGF inhibitors versus sham injection in likelihood of withdrawal due to adverse events.
- The prior USPSTF review found no significant differences between VEGF inhibitors versus sham in likelihood of ocular hemorrhage (one trial), retinal detachment (two trials), or endophthalmitis (two trials), though these events occurred infrequently and estimates were imprecise.
- Rates of cardiovascular events and other serious adverse events in the trials were low, did not differ significantly across groups, and the studies were not sufficiently powered to accurately assess these outcomes.

Newer vs. Older VEGF Inhibitors for Wet AMD

- Three new trials (N=2,738) found that serious ocular adverse events and cardiovascular events were infrequent and occurred in similar proportions of patients randomized to either aflibercept or ranibizumab.

Antioxidant Vitamins and Minerals for Dry AMD

- The AREDS trial found zinc use associated with increased risk for hospitalization due to genitourinary causes versus nonuse (7.5% vs. 4.9%, RR, 1.47, 95% CI, 1.19 to 1.80) and antioxidant use associated with increased risk of yellow skin compared with nonuse (8.3% vs. 6.0%, RR, 1.38, 95% CI, 1.09 to 1.75).
- The AREDS 2 trial found the AREDS formulation with beta carotene associated with increased risk of lung cancer versus the AREDS formulation without beta carotene (2.0% vs. 0.9%, p=0.04) when current smokers were excluded from the analysis; almost all (91%) of the lung cancers in this analysis occurred in former smokers.
- Evidence on harms of antioxidant vitamins and minerals for dry AMD was otherwise limited due to suboptimal reporting and imprecision, but did not indicate increased risk of serious adverse events or withdrawal due to adverse events.

Evidence

VEGF Inhibitors for Wet AMD

As described in the prior USPSTF review, there were no significant differences between VEGF

inhibitors versus sham treatment in likelihood of withdrawal due to adverse events in the MARINA⁹⁵ (n=716, RR, 0.88, 95% CI, 0.45 to 1.70) or VISION⁹³ trials (N=1,208, RR 1.00, 95% CI 0.27 to 3.66) (**Appendix B Table 9**). Evidence on the effects of VEGF inhibitors on other harms was limited.² Serious ocular harms were infrequent, and incidence of endophthalmitis (two trials, N=1,924; RR 5.49, 95% CI 0.30 to 99 and RR 8.33, 95% CI 0.50 to 140), ocular hemorrhage (one trial, n=184; RR 0.52, 95% CI 0.08 to 3.61), and retinal detachment (two trials, N=1,924; RR 0.17, 95% CI 0.01 to 4.07, and RR 3.67, 95% CI 0.20 to 65) were similar in VEGF and sham groups.^{2,93-95}

Rates of cardiovascular events and other serious adverse events in the trials were low, did not differ significantly across groups, and the studies were not sufficiently powered to accurately assess these outcomes (**Appendix B Table 9**).^{93-95,130} In MARINA, there was no difference between ranibizumab and sham in risk of myocardial infarction (2% vs. 2%; RR 1.12, 95% CI 0.35 to 3.60) or cerebrovascular accident (RR 2.24, 95% CI 0.49 to 10);⁹⁵ neither group in PIER experienced a myocardial infarction or cerebrovascular accident after 1 year, and one ischemic cardiomyopathy event occurred in the sham arm.⁹⁴ The VISION trials reported thromboembolic events of 6 percent in all groups.⁹³

Newer vs. Older VEGF Inhibitors for Wet AMD

Serious treatment-emergent ocular adverse events were infrequent in the VIEW trials (**Appendix B Table 9**).¹²⁷ Discontinuation due to adverse events was low in aflibercept (1.9%) and ranibizumab (1.0%) groups. Aflibercept and ranibizumab were associated with similar rates of patients with at least 1 ocular serious adverse event (2.0% vs. 3.2%, RR 0.62, 95% CI 0.36 to 10.7).¹²⁷ In RIVAL, discontinuation due to adverse events was 7.9 percent for aflibercept and 7.0 percent for ranibizumab; total ocular serious adverse effects were also low and similar across groups (2.9% vs. 1.4%, RR 2.02, 95% CI 0.38 to 10.9; **Appendix B Table 9**).¹²⁶

In the VIEW trials, intravitreal aflibercept and ranibizumab were associated with low and similar rates of vascular mortality (0.5% vs. 0.3%, RR 1.47, 95% CI 0.32 to 6.78), myocardial infarction (0.8% vs. 1%, RR 0.76, 95% CI 0.29 to 1.97), and cerebrovascular accident (0.4% vs. 0.2%, RR 2.28, 95% CI 0.28 to 18.5) after 1-year followup (**Appendix B Table 9**).¹²⁶ Two year followup from the RIVAL trial also found low and similar rates across treatment arms for atrial fibrillation (aflibercept 0% vs. ranibizumab 5.0%, RR 0.07, 95% CI 0.004 to 1.17), and cerebrovascular accidents (aflibercept 2.2% vs. ranibizumab 0.7%, RR 3.04, 95% CI 0.32 to 29).¹²⁶

Antioxidant Vitamins and Minerals for Dry AMD

The prior USPSTF review² included evidence on harms of antioxidant vitamins and minerals from the AREDS trial (**Appendix B Table 17**). Zinc use was associated with increased risk for hospitalization due to genitourinary causes versus nonuse (7.5% vs. 4.9%, RR 1.47, 95% CI, 1.19 to 1.80)¹³¹ and use of antioxidants was associated with increased risk of yellow skin compared versus nonuse (8.3% vs. 6.0%, RR 1.38, 95% CI 1.09 to 1.75).⁹⁰ None of the active treatments in AREDS (antioxidants, zinc, or both) were associated with increased risk of serious adverse events, which were uncommon (**Appendix B Table 17**). AREDS 2 found no differences between lutein and zeaxanthin versus placebo in risk of serious adverse events among persons on

the AREDS formulation. In the secondary randomization to different AREDS formulations (original formulation, without beta carotene, with low-dose zinc, or without beta carotene and without low dose zinc), there were also no differences between groups in risk of serious adverse events.¹⁰³ However, in an analysis in which current smokers were excluded, the AREDS formulation with beta carotene was associated with increased risk of lung cancer versus the AREDS formulation without beta carotene (2.0% vs. 0.9%, p=0.04). In this analysis, almost all (91%) of the lung cancers occurred in former smokers.

The largest trial after AREDS and AREDS 2, VECAT (n=1,193), reported no serious adverse events with vitamin E or placebo, and no differences in risk of withdrawal due to adverse events or specific adverse events.¹¹⁶ Evidence on harms of antioxidant vitamins and minerals for dry AMD from other trials was limited, due to suboptimal reporting and imprecision as a result of small, underpowered sample sizes.^{71,119,120} Four trials reported small numbers of withdrawals due to adverse events arms^{112,115,116,118} and two trials reported few serious adverse events;^{101,114} rates for both of these outcomes were similar for treatments and controls (**Appendix B Table 17**). Otherwise, trials provided no information on adverse events;^{105,107,117,120} stated that no adverse events were reported;^{99,104,109,119} reported minimal harms, few adverse events, or that adverse events were well tolerated;^{108,110,111,113} or reported no or few withdrawals from treatment.¹⁰⁶

Chapter 4. Discussion

Summary of Review Findings

Table 4 summarizes the evidence reviewed for this update. As in the prior review for the USPSTF, direct evidence on screening for impaired visual acuity versus no screening, delayed screening, or usual care found no benefits on vision-related or other outcomes. Three fair- to good-quality cluster-randomized trials included in the prior review for the USPSTF⁶⁵ with more than 4,700 patients found vision screening in older adults as part of a multicomponent screening intervention in primary care settings to be no more effective than no vision screening, delayed screening, or usual care.⁷³⁻⁷⁵ One additional, smaller trial (n=188) added for this update also found screening associated with no statistical significant improvement in vision-related outcomes versus no screening.⁷⁶ Potential reasons for lack of benefit in the screening trials may include high attrition, use of suboptimal screening interventions, low uptake of recommended interventions, or high rates of antecedent eye professional care.

Recent reviews of vision screening in older adults in broader (e.g., community and home-based) settings^{132,133} also found no differences between screening versus no screening in vision or vision-related outcomes. However, a number of trials in these reviews did not meet inclusion criteria for our report because they evaluated multicomponent screening interventions and did not evaluate the vision screening component separately or screening was conducted by an eye specialist.

One previously identified trial did not meet inclusion criteria because screening was performed by an optometrist and utilized methods not commonly performed in primary care (involved visual acuity, contrast sensitivity, and visual field testing; slit lamp examination; and direct ophthalmoscopy), but may provide additional information about potential harms of screening.^{134,135} It evaluated frail elderly persons (mean age 81 years) at high risk of falls (45% with fall in the last year). Like the screening trials eligible for this review, it found screening was not associated with improved visual acuity or vision-related function. However, screening was associated with increased risk of falls.^{134,135} For falls incidence, the incidence rate ratio was 1.57 (95% CI 1.20 to 2.05). For risk of one or more falls (65% vs. 50%), RR was 1.31 (95% CI 1.13 to 1.50) and for two or more falls (38% vs. 31%), RR was 1.24 (95% CI 0.99 to 1.54). Screening was also associated with an increased risk of fractures that was just above the threshold for statistical significance (10% vs. 5.7%, RR 1.74 [95% CI 0.97 to 3.11]; p=0.06). The reason for increased falls risk was unclear, but could be related to difficulty adapting to large corrections in visual acuity or use of multifocal lenses.

Conclusions regarding the suboptimal diagnostic accuracy of vision screening tests for identifying conditions associated with impaired visual acuity in primary care settings are also unchanged from the prior review for the USPSTF. The prior review for the USPSTF found that no screening question is comparable in accuracy to tests of visual acuity for identifying impaired visual acuity^{78,86,87,89,136} and that visual acuity testing with a chart is inaccurate compared to a detailed eye examination for identifying visual conditions identified on a comprehensive ophthalmological examination. Other previously reviewed studies found that the accuracy of a

computer-based screening tool was limited, and that the MDS Vision Patterns section questions performed poorly as a screening test.^{81,83} One new study found visual acuity screening using a mobile application was accurate compared to a standard ETDRS chart.⁸⁵ Studies comparing visual acuity testing to a comprehensive ophthalmological examination are difficult to interpret, as the conditions identified on examination were not necessarily associated with impaired visual acuity. For example, it is not known whether identification of cataracts or AMD prior to the development of impaired visual acuity is associated with improved clinical outcomes compared to identification after the development of early impaired visual acuity. Although visual acuity testing with a Snellen or ETDRS chart remains the most widely used tool to measure visual acuity in primary care settings, no clinically relevant reference standard exists to determine their diagnostic accuracy, in part because such tests are often considered the standard for assessing visual acuity in clinical practice. There remains insufficient evidence to assess the accuracy or utility of pinhole testing, the Amsler grid, visual acuity tests other than the Snellen or ETDRS, physical examination, or funduscopic examination performed in primary care settings.

Conclusions from the prior review for the USPSTF of strong evidence showing the effectiveness of treatments versus no treatment for common causes of impaired visual acuity also remain unchanged. The USPSTF previously determined that a very high proportion of patients experience favorable vision-related outcomes following treatment for impaired visual acuity due to refractive error and cataracts; therefore, this evidence was not re-reviewed for this update.⁶⁵ As noted in the prior review for the USPSTF, more than half of all older adults with impaired visual acuity achieve vision better than 20/40 with refractive correction,⁶ which can be done noninvasively in most cases with corrective lenses. In patients with cataracts, a large body of observational studies indicates that surgical extraction and intraocular lens implantation results in visual acuity of 20/40 or better in more than 90 percent of patients, and is associated with improvements in vision-related quality of life.¹³⁷ Correction of refractive error and cataract removal are also associated with improvement in vision-related quality of life, although randomized trials and cohort studies have not shown clear effects on measures of function, cognition, or depression.¹³⁸⁻¹⁴²

With regard to treatments for conditions associated with impaired visual acuity, this review focused on treatments for dry and wet AMD. For dry AMD, evidence showing the effectiveness of antioxidant vitamins and minerals for slowing progression of disease or improving visual acuity remains largely restricted to the large AREDS trials.^{55,90} As reported in the prior review for the USPSTF, extended (10-year) followup from AREDS indicates continued benefits beyond the originally reported (6.3 year) data.⁹⁷ The AREDS trial found zinc use associated with increased risk for hospitalizations due to genitourinary causes versus non-use¹³¹ and the AREDS 2 trial found the AREDS formulation with beta carotene associated with increased risk of lung cancer versus the AREDS formulation without beta carotene in former smokers.⁹⁷ Based on AREDS 2 and other evidence¹⁴³ indicating an association between use of beta-carotene and increased risk of lung cancer in smokers, recommendations¹⁴⁴ for current and former smokers are to avoid the AREDS formula with beta-carotene, using lutein and zeaxanthin in its place. For wet AMD, this update focused on VEGF inhibitors, which are first line treatment in most patients. As in the prior review for the USPSTF, intravitreal injection with VEGF inhibitors was associated with improvement in visual acuity-related outcomes with a relatively low incidence of serious harms, though data on effects of VEGF inhibitors on vision-related quality of life or function are

limited and inconclusive. One area of concern with VEGF inhibitors has been a potential association with increased risk of cardiovascular events.¹⁴⁵ Although randomized trials of VEGF inhibitors for AMD did not report increased risk of cardiovascular events, they were not designed to evaluate these outcomes and the number of events were small. However, several recent observational studies found no association between use of VEGF inhibitors and increased risk of cardiovascular events.¹⁴⁵⁻¹⁴⁷ An important advantage of VEGF inhibitors compared with earlier treatments such as laser photocoagulation is that they are associated with less retinal scarring compared to laser photocoagulation, which is a particularly important consideration for patients with subfoveal (central) neovascularization, and decreased recurrence compared with photodynamic therapy with verteporfin. Although we did not identify new sham-controlled trials of VEGF inhibitors, head-to-head trials^{126,127} of recently approved FDA-approved VEGF inhibitor versus older VEGF inhibitors indicated similar effects on visual acuity-related outcomes.

Limitations

Our evidence review has some limitations. First, we utilized a previously published systematic review⁷¹ on antioxidant multivitamins and minerals for dry AMD. The reliability of systematic reviews depends on how well they are designed and conducted. Therefore, we ensured that the systematic review met a quality threshold based on predefined criteria;¹⁴⁸ we also verified data abstraction of the systematic review by independently abstracting and rating the quality of trials comparing an intervention to placebo, sham treatment, or no treatment. Second, evidence on effectiveness of treatment for dry AMD relied heavily on results of a single trial - the large, well-conducted AREDS trial.⁹⁰ Third, we excluded non-English-language studies, which could introduce language bias. However, we identified no relevant non-English-language studies in literature searches or when searching reference lists. Fourth, there were too few randomized trials to perform formal assessments for publication bias with graphical or statistical methods for small sample effects. However, we did not identify unpublished trials likely to impact findings. Fifth, there was statistical heterogeneity in some pooled analyses of VEGF inhibitors versus sham. However, inconsistency was in the magnitude of benefit, not direction of effect, which favored VEGF inhibitors across studies. Because of anticipated heterogeneity, we utilized a random effects model for pooling. Sixth, trials of screening versus no screening had methodological limitations, including high attrition and use of a suboptimal screening test. In some trials, low uptake of recommended interventions or a high rate of eye specialist care prior to screening could have attenuated potential benefits. In addition, the screening trials were published between 1997 and 2006, and may not reflect outcomes that would be obtained in current clinical practice.

Emerging Issues/Next Steps

Conbercept is a VEGF inhibitor developed in China that has been evaluated in a number of randomized trials, but excluded from this review because it is not approved by the FDA.¹⁴⁹ New therapies have been investigated for their effectiveness in the treatment of AMD. The small (n=114) Age-related Maculopathy Statin Study trial of simvastatin 40 mg/day versus placebo

found that simvastatin was associated with lower risk of AMD progression after 3 years of followup, although the difference was not statistically significant (54.4% vs. 70.2%; RR, 0.78 [95% CI, 0.58 to 1.04]).¹⁵⁰ Findings from other studies have also been inconclusive.¹⁵¹ Complement inhibitors (e.g., protease inhibitors) are also being investigated for their potential effects on AMD, though initial studies have failed to improve outcomes.^{152,153} In May 2021, several ongoing trials of brolocizumab were discontinued due to higher rates of intraocular inflammation, including retinal vasculitis and retinal vascular occlusion; one of the trials was a head to head trial of brolocizumab-dbll versus aflibercept (both newer VEGF inhibitors) for AMD. The rate of retinal vasculitis, retinal artery occlusion, or severe vision loss was around 10 out of 10,000 injections. Implications for the role of brolocizumab-dbll in treatment for AMD are uncertain.¹⁵⁴

Relevance for Priority Populations

The focus of this review was on screening in older adults, a priority population at particular risk for impaired visual acuity as well as sequelae from impaired visual acuity. Although Black males are at higher risk of unoperated cataracts, there is no evidence to suggest that cataract surgery is less successful in this patient group. Low socioeconomic status is associated with poorer access to vision services.

Future Research

Important gaps remain in the evidence on screening for impaired visual acuity in older adults. Direct evidence indicates that vision screening in older adults is not effective for improving visual outcomes or other clinical outcomes. However, in some screening trials, including the largest study, only half of patients received recommended interventions, which could have attenuated benefits.⁷⁵ In addition, vision screening was evaluated as part of a multicomponent intervention. Well-designed studies in contemporary primary care settings that evaluate more focused vision screening interventions, utilize strategies to link screen-positive older adults to appropriate followup and care, address barriers to linkage to care, and target higher-risk populations would be useful for clarifying potential benefits of screening. Screening strategies targeted at identification of AMD may be particularly suitable for future studies, given the potential for irreversible effects with delayed diagnosis. Studies are needed on diagnostic accuracy and utility of funduscopic examination, pinhole testing, the Amsler grid, and nonSnellen visual acuity charts in primary care settings for supplementing or replacing standard visual acuity eye chart. Research would also be helpful for determining the feasibility and accuracy of alternative screening modalities to supplement standard visual acuity testing in primary care settings, such as tests for dark adaptation, visual contrast, or useful field of view. Telehealth approaches to screening that could potentially facilitate access are especially relevant in the post-COVID-19 era¹⁵⁵ and warrant research consideration. Evidence on the effectiveness of antioxidant vitamins and minerals for the treatment of dry AMD remains largely dependent on the large AREDS trial⁹⁰ and could be strengthened by other large, well-designed trials of alternative regimens designed to adequately evaluate benefits and harms. Research is also needed to understand the effects of treatment for wet and dry AMD on quality of life and function. More

studies are needed to understand the potential association between correction of refractive errors and risk of falls,¹³⁵ and, if an association is present, to identify methods for mitigating these risks (e.g., avoid large corrections in visual acuity, education or training with multifocal lens). Head-to-head trials of the recently FDA-approved VEGF brolucizumab-dblb versus older VEGF inhibitors would be helpful for clarifying benefits and harms, particularly with regard to risk of adverse events related to intraocular inflammation.

Conclusions

Impaired visual acuity is common in older adults and effective treatments are available for common causes of impaired visual acuity. Visual acuity testing is the reference standard for identifying impaired visual acuity but has low diagnostic accuracy compared with an ophthalmological exam for identifying visual conditions not necessarily associated with impaired visual acuity; screening questions have low diagnostic accuracy compared with visual acuity testing. Direct evidence found no significant difference between vision screening in older adults in primary care settings versus no screening in visual acuity-related outcomes or other clinical outcome.

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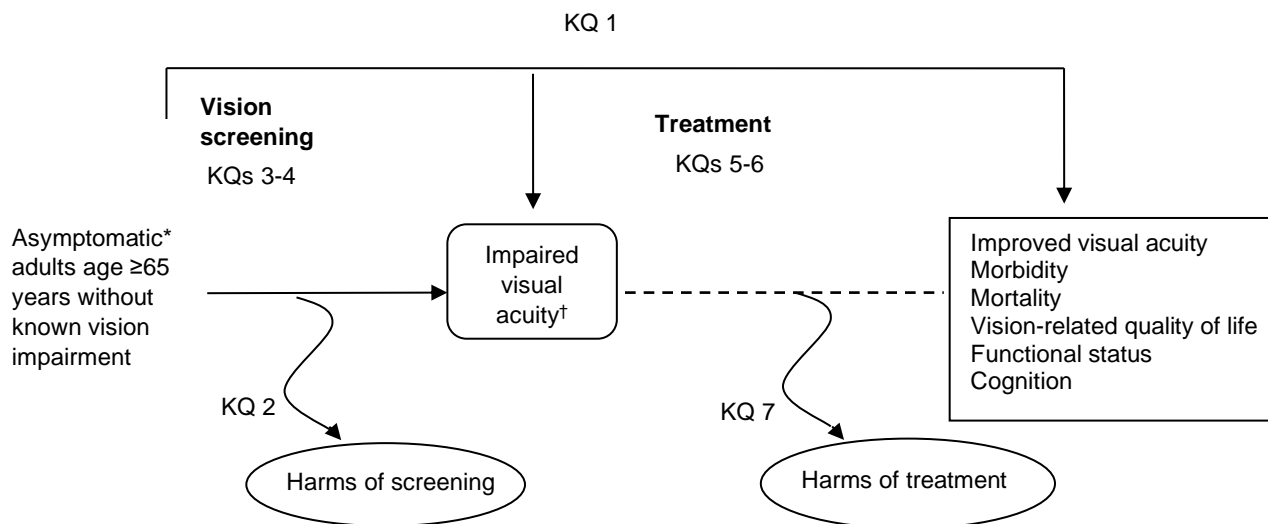
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Figure 1. Analytic Framework and Key Questions – Impaired Visual Acuity



* “Asymptomatic” individuals are defined as those without known impaired visual acuity (based on current corrected vision) who have not sought care for evaluation of vision problems.

†Conditions of interest include impaired visual acuity due to uncorrected refractive errors, cataracts, and age-related macular degeneration.

Note: Subpopulations of interest include those defined by age, sex, race/ethnicity, setting (e.g., rural or urban), and functional and cognitive status, etc.

Abbreviation: KQ = key question.

Key Question 1. What are the effects of vision screening in asymptomatic older adults versus no screening on visual acuity, morbidity or mortality, general or vision-related quality of life, functional status, or cognition?

Key Question 2. What are the harms of vision screening in asymptomatic older adults versus no screening?

Key Question 3. What is the diagnostic accuracy of screening for impaired visual acuity due to uncorrected refractive error, cataracts, or age-related macular degeneration?

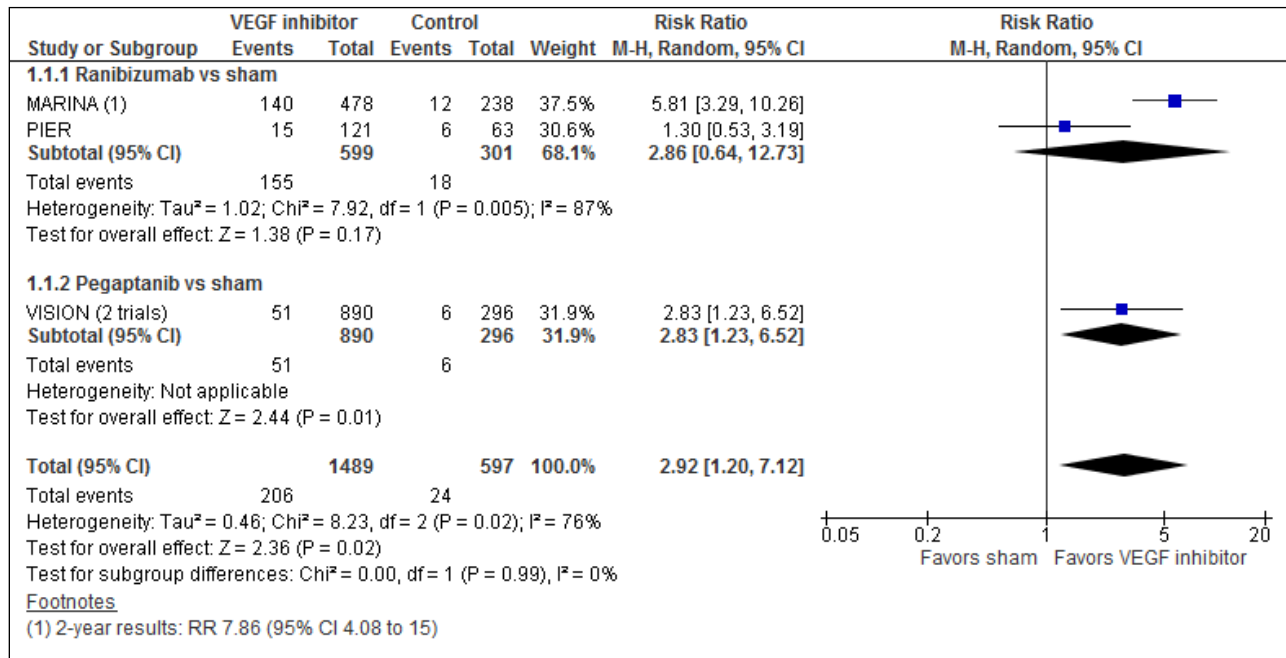
Key Question 4. What is the accuracy of instruments for identifying patients at higher risk of impaired visual acuity due to uncorrected refractive error, cataracts, or age-related macular degeneration?

Key Question 5. What are the effects of treatment for wet or dry age-related macular degeneration versus placebo or no treatment on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?

Key Question 6. What are the effects of newer (aflibercept or brolucizumab-dbl) versus older vascular endothelial growth factor inhibitors for wet age-related macular degeneration on visual acuity, morbidity, mortality, general or vision-related quality of life, functional status, or cognition?

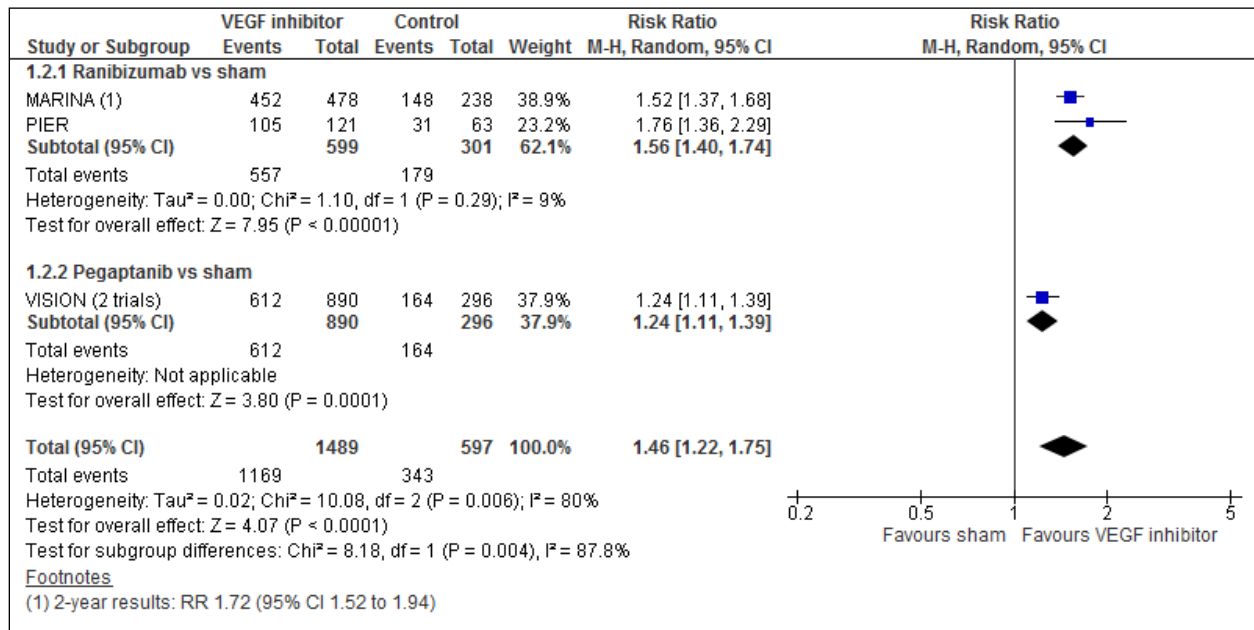
Key Question 7. What are the harms of treatment for early impaired visual acuity due to wet or dry age-related macular degeneration?

Figure 2. ≥ 15 Letters of Visual Acuity Gain With Use of VEGF Inhibitors at 1-Year Followup



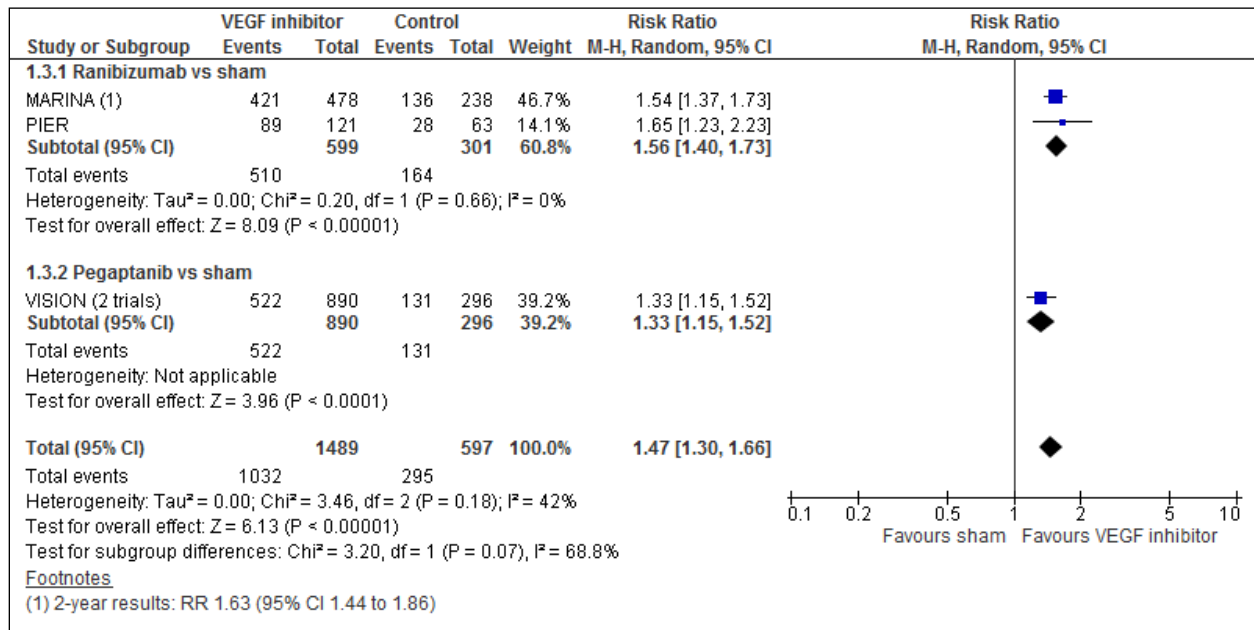
Abbreviations: CI = confidence interval; df = degrees of freedom; MARINA = minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular age-related macular degeneration; M-H = Mantel-Haenszel; PIER = phase IIIB, multicenter, randomized double-masked sham injection-controlled study of the efficacy and safety of ranibizumab; RR = risk ratio; VEGF = vascular endothelial growth factor; VISION = VEGF inhibition study in ocular neovascularization.

Figure 3. <15 Letters of Visual Acuity Loss With Use of VEGF Inhibitors at 1-Year Followup



Abbreviations: CI = confidence interval; df = degrees of freedom; MARINA = minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular age-related macular degeneration; M-H = Mantel-Haenszel; PIER = phase IIIB, multicenter, randomized double-masked sham injection-controlled study of the efficacy and safety of ranibizumab; RR = risk ratio; VEGF = vascular endothelial growth factor; VISION = VEGF inhibition study in ocular neovascularization.

Figure 4. Visual Acuity of 20/200 or Better With Use of VEGF Inhibitors at 1-Year Followup



Abbreviations: CI = confidence interval; df = degrees of freedom; MARINA = minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular age-related macular degeneration; M-H = Mantel-Haenszel; PIER = phase IIIB, multicenter, randomized double-masked sham injection-controlled study of the efficacy and safety of ranibizumab; RR = risk ratio; VEGF = vascular endothelial growth factor; VISION = VEGF inhibition study in ocular neovascularization.

Table 1. Measurements of Visual Acuity

Snellen		Decimal	LogMAR
Feet	Meters		
20/20	6/6	1.00	0.00
20/30	6/9	0.67	0.18
20/40	6/12	0.50	0.30
20/60	6/18	0.33	0.48
20/80	6/24	0.25	0.60
20/100	6/30	0.20	0.70
20/160	6/48	0.13	0.90
20/200	6/60	0.10	1.00

Note: Visual impairment is 20/50 or worse; legal blindness is 20/200 or worse.

Abbreviation: LogMAR = logarithmic minimum angle of resolution.

Source: Holladay 2004.¹⁵⁶

Table 2. Recommendations of Other Groups

Organization	Recommendation/Clinical Guidance
American Academy of Ophthalmology ⁶⁷	Patients age 65 years or older without risk factors for eye disease (e.g., diabetes, glaucoma) should have comprehensive medical eye evaluations every 1 to 2 years.
American Optometric Association ⁶⁸	Annual comprehensive eye and vision examinations are recommended for persons 65 years of age or older for the diagnosis and treatment of sight-threatening eye conditions and the timely correction of refractive errors.
American Academy of Family Physicians ⁶⁹	Links to the 2016 U.S. Preventive Services Task Force Recommendation.

Table 3. Screening Trials

Author, Year	Intervention	Screening Tools	Results
Eekhof, 2000 ^{73,78} <i>From prior report</i>	A. Vision screening (n=576) B. Delayed screening (n=545)	Validated diagnostic tests: Assessment of difficulty in recognizing a face at 4 meters and/or reading normal letters in a newspaper, and/or impaired vision with both by Snellen eye chart or not being able to read normal newspaper letters at 25 centimeter distance Vision was measured with the glasses usually worn	A vs. B Vision disorder detected: 49% (95% CI 43% to 54%) vs. NR Visual disorder in 2nd year: 51% (95% CI 45% to 58%) vs. 47% (95% CI 42% to 52%); p=0.68
Moore, 1997 ⁷⁴ <i>From prior report</i>	A. Vision screening, coupled with clinical summaries (n=112) B. Usual care (n=149)	Question, "Do you have difficulty driving or watching television or reading or doing any of your daily activities because of your eyesight (even while wearing glasses)?", followed by Snellen eye chart if positive	A vs. B Vision problem detected: 20% vs. 19%, p=0.84 Improvement in vision at 6 months: 20% (20/99) vs. 24% (31/131); RR 0.85 (95% CI 0.52 to 1.40)
Smeeth, 2003 ⁷⁵ MRC Trial <i>From prior report</i>	A. Universal screening = brief health assessment plus detailed health assessment, latter of which included measurement of VA (n=1,565) B. Targeted screening = brief health assessment (n=1,684, 120 of which had a detailed assessment due to severity of problems, though 150 were eligible)	Detailed health assessment: VA measured using Glasgow acuity eye chart (Snellen equivalent provided in results), and pinhole testing if VA less than 6/18 in either eye; referral to ophthalmologist when appropriate Brief health assessment: Covered all areas specified in the general practitioner contract, including a question about difficulty seeing, but did not include measurement of VA. Those with a specified range and level of problems were eligible to have a detailed assessment Note: reporting difficulty seeing was not on its own sufficient to lead to a detailed assessment	A vs. B Found to have VA <6/18 (20/60) in either eye: 29% (451/1565) vs. 3.1% (53/1684) Eligible for referral to ophthalmologist: 14% (220/1565) vs. 1.7% (29/1684) Eligible for referral to optician: 5% (79/1565) vs. 0.4% (8/1684) At followup: VA <6/18 (20/60) in either eye at 3 years: 37% (307/829) vs. 35% (339/978), RR 1.07 (95% CI 0.84 to 1.36) VA <6/18 binocular vision: 14% (114/817) vs. 17% (160/962), RR 0.84 (95% CI 0.64 to 1.10) VA <6/12 in either eye: 59% (486/829) vs. 60% (584/978), RR 0.98 (95% CI 0.82 to 1.17) VA <6/12 binocular vision: 31% (256/817) vs. 37% (351/962), RR 0.86 (95% CI 0.65 to 1.13) NEI-VFQ mean composite score (scale 0 to 100; higher score = better quality of life): 86.0 vs. 85.6; mean difference 0.4 (95% CI -1.7 to 2.5)
Tay, 2006 ⁷⁶ ACCS <i>Added</i>	Routine aged care assessment and interview using a standardized questionnaire, plus: A. Vision screening (n=96) B. No vision screening (n=92)	LogMAR chart for presenting VA for distance (with glasses, if worn) using letters read correctly using ETDRS-Fast protocol Binocular near vision and visual field using confrontation method Self-report questions: Did you notice any deterioration in one or both eyes? Are you able to recognize a friend across the street? Can you read the ordinary print in the newspaper reasonably well, with or without glasses?	A vs. B Mean VA: 39 letters vs. 35 letters, p=0.25 Bilateral visual impairment: 35% vs. 47%, p=0.17

Abbreviations: ACCS = Aged Care Client pilot Study; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LogMAR = logarithmic minimum angle of resolution; MRC = Medical Research Council; NEI-VFQ = National Eye Institute Visual Function Questionnaire; NR = not reported; RR = relative risk; VA = visual acuity.

Table 4. Summary of Evidence

Key Question	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of evidence	Applicability
KQ 1. Benefits of screening	k=4 trials (3 in prior USPSTF review, 1 new) N=4,819	Four trials of screening versus no screening, usual care, or delayed screening in older adults found no difference on vision or other clinical outcomes in older adults.	Evidence was consistent and reasonably precise	All studies rated fair quality; interventions and comparators differed across studies; adherence with recommended follow-up and interventions was low in some trials; attrition high in some trials Reporting bias not detected.	Moderate for no benefit	Screening tests feasible for primary care; the studies were conducted in the United States., Europe, and Australia; screening conducted in community or general practice settings or a geriatric day hospital; screening conducted by general practitioners, office staff, or trained nurses; vision screening was conducted as part of a multicomponent health screen
KQ 2. Harms of screening	No studies	No included trials reported harms of screening.	-	-	Insufficient	-
KQ 3. Diagnostic accuracy of screening tests	K= 8 cross-sectional studies (7 in prior USPSTF review, 1 new) N= 7,398	Visual acuity tests (3 studies) were associated with poor diagnostic accuracy for identifying visual conditions compared with a complete examination by an ophthalmologist; evidence on other screening tests was limited.	Evidence was consistent and precise.	All studies rated fair-quality; variability in screening tests and testing thresholds; test threshold not specified in some studies; clinical relevance of visual conditions identified on ophthalmological examination but not associated with impaired visual acuity unclear; some screening tests have not been validated Reporting bias not detected	Moderate	Screening tests were feasible for primary care; studies were conducted in the United States, United Kingdom, and Australia; variability in screening settings (primary care clinics, general eye clinics, hospitals, community day centers, and nursing homes); screener trained research staff or unclear in some studies

Table 4. Summary of Evidence

Key Question	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of evidence	Applicability
KQ 4. Diagnostic accuracy of screening instruments	K= 3 cross-sectional studies (2 in prior USPSTF review, 1 new) N= 5,203	Three studies found that a screening question was not accurate for identifying older persons with impaired visual acuity compared with a visual acuity chart	Evidence was consistent and reasonably precise.	All studies rated fair-quality; the screening question varied across studies Reporting bias not detected	Moderate	The screening questions were highly feasible for primary care; studies were conducted in the United States and Europe.
KQ 5. Benefits of treatment for AMD vs. placebo/no treatment <i>Wet AMD - VEGF Inhibitors</i>	k= 4 trials (all in prior USPSTF review) N= 2,086	Four trials of VEGF inhibitors were associated with greater likelihood of ≥ 15 letters (3 lines) of visual acuity gain (RR, 2.92, 95% CI 1.20 to 7.12; $I^2=76\%$; ARD10%), <15 letters (3 lines) of visual acuity loss (RR 1.46, 95% CI 1.22 to 1.75, $I^2=80\%$; ARD 27%), and having vision 20/200 or better (RR, 1.47, 95% CI, 1.30 to 1.66, $I^2=42\%$; ARD 24%) at 1 year versus sham injection. In 1 trial, VEGF inhibitors were associated with better vision-related function and quality of life measures versus sham injection at 1 and 2 years, the mean difference was above the threshold for a minimum clinically important difference	Consistent (statistical heterogeneity present in pooled analyses, but inconsistency was in magnitude of effect, not direction of effect) Precise	Data on function or quality of life limited to 1 trial; studies not designed to evaluate mortality or other health outcomes Reporting bias was not detected	Moderate for benefit	VEGF inhibitors are considered first-line therapy in the United States; baseline visual acuity 20/80 in 3 studies and ranged from 20/40 to 20/200 in 1 study; studies were conducted in the United States in 2 trials, and the others had various sites (United States, Canada, Europe, Israel, Australia, South America).

Table 4. Summary of Evidence

Key Question	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of evidence	Applicability
<p>KQ 5. Benefits of treatment for AMD vs. placebo/no treatment</p> <p><i>Dry AMD – Vitamin and Mineral Supplements</i></p>	<p>k=1 systematic review of 19 trials (N=11,162) and 2 additional trials N=180</p> <p>The prior USPSTF review included a prior version of the SR with 13 trials</p>	<p>Antioxidant multivitamins associated with decreased risk of progression to late AMD (3 trials, N=2,445 people, OR 0.72 [95% CI 0.58 to 0.90]) and ≥ 3 lines visual acuity loss (1 trial, N=1,791 people, OR 0.77 [95% CI 0.62 to 0.96]) versus placebo. Zinc was associated with decreased risk of progression to late AMD versus placebo (3 trials, N=3,790 people, OR 0.83 [95% CI 0.70 to 0.98]; 96% of patients from AREDS) and decreased risk of visual acuity loss ≥ 3 lines that was of borderline statistical significance (2 trials, 3,791 people, RR 0.87 [95% CI 0.75 to 1.00]).</p>	<p>Evidence was consistent and precise.</p>	<p>Findings were primary based on 1 study (AREDS); heterogeneity in the interventions assessed</p>	<p>Moderate for benefit</p>	<p>AREDS was conducted in the United States and the AREDS and AREDS 2 formulations are widely used in clinical practice; baseline visual acuity was 20/32 or better in AREDS; ~75% of patients in AREDS had mild to moderate AMD at baseline</p>
<p>KQ 6. Benefits of newer (aflibercept or brolucizumab-dbl) versus older VEGF inhibitors for AMD</p>	<p>k= 3 trials (all new) N= 2,738</p>	<p>Aflibercept was noninferior to ranibizumab in likelihood of <15 ETDRS letters of visual acuity loss (3 trials), ≥ 15 letters of visual acuity gain (3 trials), and similar to ranibizumab for vision-related function (2 trials).</p>	<p>Evidence was consistent and reasonably precise</p>	<p>No trial of brolucizumab-dbl met inclusion criteria; trials not designed to assess mortality or other health outcomes.</p> <p>Reporting bias was not detected</p>	<p>Moderate for similar benefit</p>	<p>Aflibercept was FDA approved for AMD in 2011, and with a longer dosing schedule in 2018; One trial was conducted in Australia, and the others had various sites (United States, Canada, international)</p>

Table 4. Summary of Evidence

Key Question	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of evidence	Applicability
<p>KQ 7. Harms of treatment for AMD</p> <p><i>Wet AMD – VEGF Inhibitors</i></p>	<p>VEGF vs. sham: k= 4 trials (all in prior USPSTF review) N= 2,086</p> <p>Newer vs. older VEGF: k= 3 trials (all new) N= 2,738</p>	<p>No differences between VEGF inhibitors versus sham injection in likelihood of withdrawal due to adverse events, cardiovascular events, or serious ocular adverse events</p> <p>Three trials found that serious ocular adverse events were infrequent and occurred in similar proportions of patients randomized to either aflibercept or ranibizumab.</p>	<p>Evidence was consistent and imprecise.</p>	<p>Trials not powered for serious cardiovascular or ocular adverse events.</p> <p>Reporting bias not detected</p>	<p>Moderate for no harm</p>	<p>VEGF vs. sham: VEGF inhibitors are considered first-line therapy in the United States; baseline visual acuity 20/80 in 3 studies and ranged from 20/40 to 20/200 in 1 study; studies were conducted in the United States in 2 trials, and the others had various sites (United States, Canada, Europe, Israel, Australia, South America)</p> <p>Newer vs. older VEGF: Aflibercept was FDA approved for AMD in 2011, and with a longer dosing schedule in 2018; One trial was conducted in Australia, and the others had various sites (United States, Canada, international)</p>

Table 4. Summary of Evidence

Key Question	Studies (k) Observations (n) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of evidence	Applicability
<p>KQ 7. Harms of treatment for AMD</p> <p><i>Dry AMD – Vitamin and Mineral Supplements</i></p>	<p>k=1 systematic review of 19 trials (N=11,162) and 2 additional trials N=180</p> <p>The prior USPSTF review included a prior version of the SR with 13 trials</p>	<p>The AREDS trial found zinc use associated with increased risk for hospitalization due to genitourinary causes versus nonuse (7.5% vs. 4.9%, RR, 1.47 [95% CI, 1.19 to 1.80]) and antioxidant use associated with increased risk of yellow skin compared with nonuse (8.3% vs. 6.0%, RR, 1.38 [95% CI, 1.09 to 1.75). The AREDS 2 trial found the AREDS formulation with beta carotene associated with increased risk of lung cancer versus the AREDS formulation without beta carotene (2.0% vs. 0.9%, p=0.04); almost all (91%) of the lung cancers in this analysis occurred in former smokers (current smokers were excluded from the analysis). Evidence on harms of antioxidant vitamins and minerals for dry AMD was otherwise limited, but did not indicate increased risk of serious adverse events or withdrawal due to adverse events.</p>	<p>Evidence was consistent. Evidence was precise for the AREDS formulation but imprecise for other antioxidant multivitamins and minerals</p>	<p>Trials were not designed to evaluate harms and reporting of harms from some trials was suboptimal</p>	<p>Moderate for harm (for AREDS formulation)</p>	<p>AREDS was conducted in the United States and the AREDS and AREDS 2 formulations are widely used in clinical practice; baseline visual acuity was 20/32 or better in AREDS; ~75% of patients in AREDS had mild to moderate AMD at baseline</p>

Abbreviations: AMD = age-related macular degeneration; ARD = absolute risk difference; AREDS = Age-Related Eye Disease Studies; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; FDA = United States Food and Drug Administration; KQ = key question; OR = odds ratio; RR = risk ratio; SR = systematic review; USPSTF = United States Preventive Services Task Force; VEGF = vascular endothelial growth factor.

Appendix A1. Search Strategies

Database: Ovid MEDLINE(R) ALL

Screening

- 1 Vision Screening/
- 2 exp Vision Tests/
- 3 exp Refractive Errors/
- 4 exp Vision Disorders/
- 5 exp Macular Degeneration/
- 6 exp Cataract/
- 7 (vision or presbyop\$ or myop\$ or astigmati\$ or hyperop\$ or cataract\$ or "macular degeneration" or "armd" or "amd").ti,ab,kf.
- 8 Mass Screening/
- 9 screen*.ti,ab,kf.
- 10 or/2-7
- 11 or/8-9
- 12 10 and 11
- 13 1 or 12
- 14 13 not (adolescens\$ or child\$ or school or pediatric\$ or toddler or infant\$ or newborn or neonat\$ or prematur\$).ti,ab.
- 15 14 not "diabetic retinopathy".ti.
- 16 limit 15 to yr="2015 -Current"
- 17 (random* or control* or trial or cohort or case* or prospective or retrospective or systematic or "meta analysis" or "metaanalysis").ti,ab,kf,tw,pt,sh.
- 18 (canine or dog or dogs or mouse or mice or rat or rats).ti.
- 19 16 and 17
- 20 19 not 18
- 21 limit 20 to english language

Diagnostic Accuracy

1. Vision Screening/
2. exp Vision Tests/
3. exp Refractive Errors/
4. exp Vision Disorders/
5. exp Macular Degeneration/
6. exp Cataract/
7. (presbyop\$ or myop\$ or astigmati\$ or hyperop\$ or cataract\$ or "macular degeneration" or "armd" or "amd").ti,ab,kf.
8. or/1-7
9. (screen* or test*).ti,ab,kf.
10. 8 and 9
11. exp "Sensitivity and Specificity"/
12. (sensitivity or specificity or accuracy or predict*).ti,ab,kf.
13. 11 or 12
14. 10 and 13
15. 14 not (adolescens* or child* or school or preschool* or pediatric\$ or paediatric* or toddler or infant* or newborn or neonat* or prematur*).ti,ab.

Appendix A1. Search Strategies

16. 15 not "diabetic retinopathy".ti,ab.
17. limit 16 to yr="2015 -Current"
18. 17 not (canine or dog or dogs or mouse or mice or rat or rats).ti.
19. limit 18 to english language

Treatment

- 1 exp Macular Degeneration/dh, dt, pc
- 2 ("macular degeneration" or "ARMD" or "AMD").ti,ab,kf.
- 3 Ranibizumab/
- 4 Bevacizumab/
- 5 (ranibizumab or pegaptanib or aflibercept or brolucizumab or bevacizumab).ti,ab,kf.
- 6 exp Vitamins/
- 7 exp Antioxidants/
- 8 Dietary Supplements/
- 9 (vitamin* or antioxidant* or zinc or "beta carotene" or copper or lutein or "eicosapentaenoic acid" or "docosahexaenoic acid" or zeaxanthin or "fish oil").ti,ab,kf.
- 10 AREDS.ti,ab.
- 11 1 or 2
- 12 or/3-10
- 13 11 and 12
- 14 limit 13 to yr="2015 -Current"
- 15 (random* or control* or trial or cohort or case* or prospective or retrospective or systematic or "meta analysis" or "metaanalysis").ti,ab,kf,tw,pt,sh.
- 16 14 and 15
- 17 limit 16 to english language

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

Screening

- 1 Vision Screening/
- 2 exp Vision Tests/
- 3 exp Refractive Errors/
- 4 exp Vision Disorders/
- 5 exp Macular Degeneration/
- 6 exp Cataract/
- 7 (vision or presbyop\$ or myop\$ or astigmati\$ or hyperop\$ or cataract\$ or "macular degeneration" or "armd" or "amd").ti,ab,hw.
- 8 Mass Screening/
- 9 screen*.ti,ab,hw.
- 10 or/2-7
- 11 or/8-9
- 12 10 and 11
- 13 1 or 12
- 14 13 not (adolescen\$ or child\$ or school or pediatric\$ or toddler or infant\$ or newborn or neonat\$ or prematur\$).ti,ab.
- 15 14 not "diabetic retinopathy".ti.

Appendix A1. Search Strategies

- 16 limit 15 to yr="2015 -Current"
- 17 conference abstract.pt.
- 18 "journal: conference abstract".pt.
- 19 "journal: conference review".pt.
- 20 "http://.www.who.int/trialsearch*".so.
- 21 "https://clinicaltrials.gov*".so.
- 22 or/17-21
- 23 16 not 22

Diagnostic Accuracy

- 1 Vision Screening/
- 2 exp Vision Tests/
- 3 exp Refractive Errors/
- 4 exp Vision Disorders/
- 5 exp Macular Degeneration/
- 6 exp Cataract/
- 7 (presbyop\$ or myop\$ or astigmati\$ or hyperop\$ or cataract\$ or "macular degeneration" or "armd" or "amd").ti,ab,hw.
- 8 or/1-7
- 9 (screen* or test*).ti,ab,hw.
- 10 8 and 9
- 11 exp "Sensitivity and Specificity"/
- 12 (sensitivity or specificity or accuracy or predict*).ti,ab,hw.
- 13 11 or 12
- 14 10 and 13
- 15 14 not (adolescen* or child* or school or preschool* or pediatric\$ or paediatric* or toddler or infant* or newborn or neonat* or prematur*).ti,ab.
- 16 15 not "diabetic retinopathy".ti,ab.
- 17 limit 16 to yr="2015 -Current"
- 18 17 not (canine or dog or dogs or mouse or mice or rat or rats).ti.
- 19 limit 18 to english language
- 20 conference abstract.pt.
- 21 "journal: conference abstract".pt.
- 22 "journal: conference review".pt.
- 23 "http://.www.who.int/trialsearch*".so.
- 24 "https://clinicaltrials.gov*".so.
- 25 20 or 21 or 22 or 23 or 24
- 26 19 not 25

Treatment

1. exp Macular Degeneration/dh, dt, pc
2. ("macular degeneration" or "ARMD" or "AMD").ti,ab,hw.
3. Ranibizumab/
4. Bevacizumab/
5. (ranibizumab or pegaptanib or aflibercept or brolocizumab or bevacizumab).ti,ab,hw.
6. exp Vitamins/

Appendix A1. Search Strategies

7. exp Antioxidants/
8. Dietary Supplements/
9. (vitamin* or antioxidant*).ti,ab,hw.
10. (zinc or "beta carotene" or copper or lutein or "eicosapentaenoic acid" or "docosahexaenoic acid" or zeaxanthin or "fish oil").ti,ab,hw.
11. AREDS.ti,ab.
12. 1 or 2
13. or/3-11
14. 12 and 13
15. limit 14 to yr="2015 -Current"
16. limit 15 to english language
17. conference abstract.pt.
18. "journal: conference abstract".pt.
19. "journal: conference review".pt.
20. "http://.www.who.int/trialsearch*".so.
21. "https://clinicaltrials.gov*".so.
22. 17 or 18 or 19 or 20 or 21
23. 16 not 22

Database: EBM Reviews - Cochrane Database of Systematic Reviews

All KQs

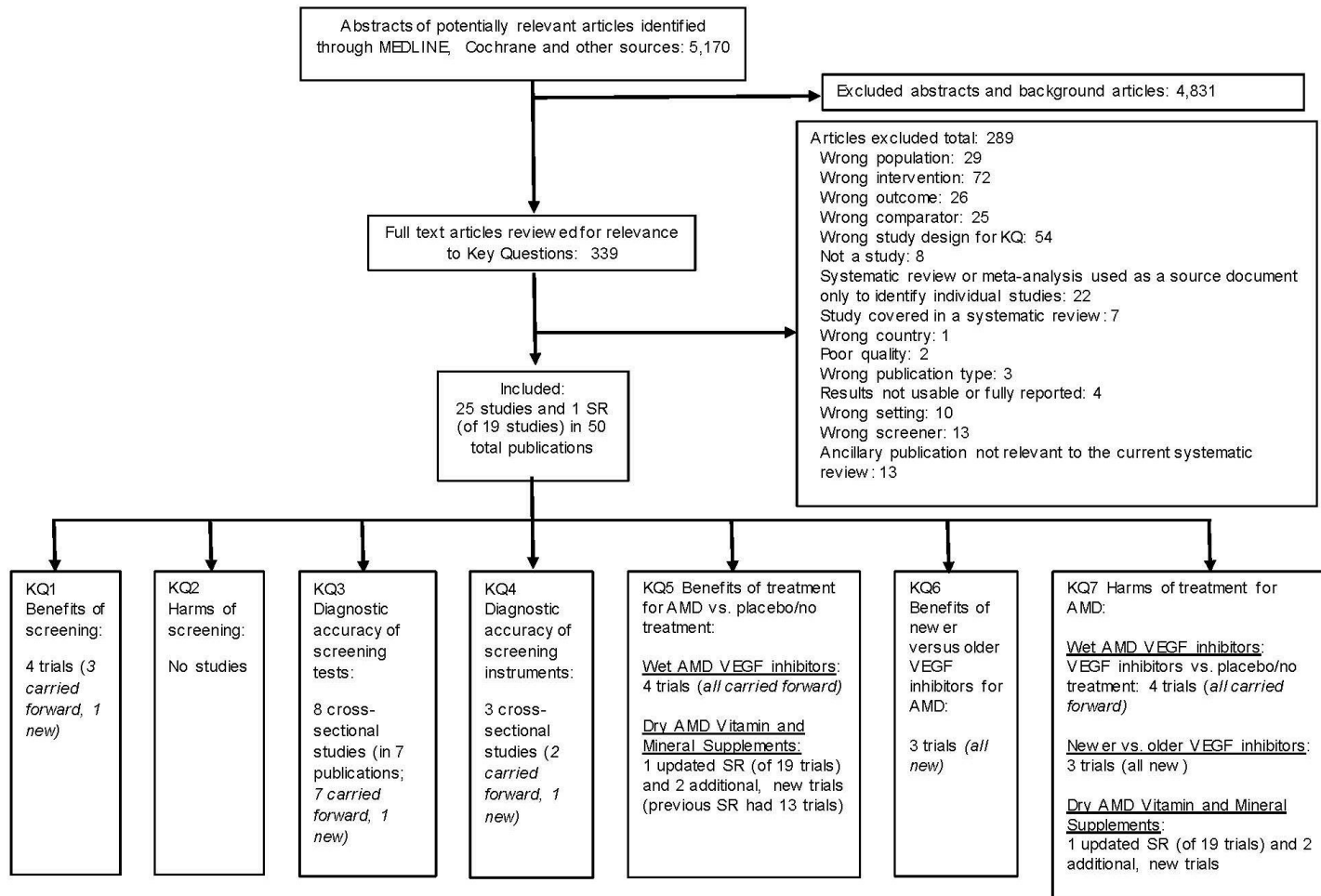
- 1 (vision or presbyop\$ or myop\$ or astigmati\$ or hyperop\$ or cataract\$ or "macular degeneration" or "armd" or "amd").ti,ab.
- 2 "eyes and vision".gw.
- 3 1 and 2
- 4 limit 3 to last 5 years
- 5 limit 4 to full systematic reviews
- 6 5 not child*.ti.
- 7 screen*.ti,ab.
- 8 6 and 7
- 9 (sensitivity or specificity or accuracy or predict*).ti,ab.
- 10 6 and 9
- 11 ("macular degeneration" or "armd" or "amd").ti,ab.
- 12 8 or 10 or 11

Appendix A2. Inclusion and Exclusion Criteria

	Include	Exclude
Definition of Disease	Impaired VA due to uncorrected refractive errors, cataracts, or AMD for screening and due to AMD for treatment	Impaired VA due to other conditions
Populations	<p>KQs 1-4: Asymptomatic adults 65 years of age and older without known impaired VA (based on current corrected vision) and who have not sought care for evaluation of vision problems</p> <p>KQs 5-7: Asymptomatic adults with vision impairment (current corrected VA worse than 20/40 but better than 20/200) due to uncorrected refractive errors (myopia, hyperopia, astigmatism, or presbyopia), AMD, or cataracts</p>	<p>KQs 1-4: Known impaired VA based on current corrected vision or who have sought care for evaluation of vision problems</p> <p>KQs 5-7: VA worse than 20/200, other causes of vision loss</p>
Interventions	<p>KQs 1-2: Vision screening performed in primary care or community-based settings, including multi-component screening with a distinct vision screening component</p> <p>KQs 3-4: Vision screening tests performed in primary care or community-based settings; questions or questionnaires for impaired VA</p> <p>KQs 5-7: For wet AMD, vascular endothelial growth factor inhibitors (ranibizumab, pegaptanib, aflibercept, brolucizumab-dbl, and bevacizumab); for dry AMD, vitamins and antioxidants</p>	<p>KQs 1-2: Vision screening performed in eye specialty settings</p> <p>KQs 3-4: Diagnostic tests for vision screening performed in eye specialty settings (including fundoscopic examination performed by an eye professional and specialized diagnostic testing)</p> <p>KQs 5-7: Laser photocoagulation, photodynamic therapy, treatment for uncorrected refractive error and cataracts</p>
Comparisons	<p>KQs 1-2: No screening</p> <p>KQs 3-4: Reference standard for impaired VA (as defined in the studies)</p> <p>KQs 5, 7: No treatment or placebo</p> <p>KQ 6: Newer (aflibercept or brolucizumab-dbl) versus older vascular endothelial growth factor inhibitors</p>	
Outcomes	<p>KQs 1-2, 5-7: VA; vision-related quality of life; functional capacity, including ability to drive and driving outcomes; other measures of morbidity; mortality; cognition; harms, including falls and fractures; other treatment-related harms</p> <p>KQs 3-4: Sensitivity, specificity, positive and negative predictive values, areas under the receiver operating curve, other measures of diagnostic test accuracy</p>	KQs 1-2, 5-7: Reading speed and other tests of vision function
Setting	United States applicable, primary care relevant	-
Study Designs	<p>KQs 1-2: RCTs and controlled observational studies comparing vision screening to no screening, delayed screening or usual care (i.e., targeted screening)</p> <p>KQs 3-4: Studies evaluating diagnostic accuracy of a screening question or diagnostic test compared to a reference standard</p> <p>KQs 5-7: RCTs comparing treatment to no treatment (including sham injection); controlled observational studies will be included if evidence on harms from RCTs is insufficient</p>	-
Study Quality	Fair or good quality studies	Poor quality studies

Abbreviations: AMD = age-related macular degeneration; KQ = key question; RCTs = randomized controlled trials; VA = visual acuity.

Appendix A3. Literature Flow Diagram



Abbreviations: AMD = Age-Related Macular Degeneration; AREDS = Age-Related Eye Disease Studies; KQ = key question; SR = systematic review; VEGF = vascular endothelial growth factor.

Note: The number of included studies does not total to the number shown, because some studies are included for more than one Key Question.

Appendix A4. Included Studies

1. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. 2013;309(19):2005-15. doi: 10.1001/jama.2013.4997. PMID: 23644932.
2. AREDS Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 2001;119(10):1417-36. PMID: 11594942.
3. Ariyasu RG, Lee PP, Linton KP, et al. Sensitivity, specificity, and predictive values of screening tests for eye conditions in a clinic-based population. *Ophthalmology*. 1996;103(11):1751-60.
4. Arora KS, Chang DS, Supakontanasan W, et al. Assessment of a rapid method to determine approximate visual acuity in large surveys and other such settings. *Am J Ophthalmol*. 2014;157(6):1315-21.e1. doi: 10.1016/j.ajo.2014.02.031. PMID: 24548874.
5. Bartlett HE, F.A. E. Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular degeneration: a randomized controlled trial. *Eur J Clin Nutr*. 2007;61(9):1121-7.
6. Beatty S, Chakravarthy U, Nolan JM, et al. Secondary outcomes in a clinical trial of carotenoids with coantioxidants versus placebo in early age-related macular degeneration. *Ophthalmology*. 2013;120(3):600-6. doi: 10.1016/j.ophtha.2012.08.040. PMID: 23218821.
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9. Chang TS, Bressler NM, Fine JT, et al. Improved vision-related function after ranibizumab treatment of neovascular age-related macular degeneration: results of a randomized clinical trial. *Arch Ophthalmol*. 2007;125(11):1460-9. PMID: 17998507.
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11. Chew EY, Clemons TE, Agron E, et al. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: the AREDS2 Randomized Clinical Trial. *JAMA*. 2015;314(8):791-801. doi: 10.1001/jama.2015.9677. PMID: 26305649.
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Appendix A5. Excluded Studies

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2. Abraham P, Yue H, Wilson L. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2. *Am J Ophthalmol*. 2010;150(3):315-24.e1. doi: 10.1016/j.ajo.2010.04.011. PMID: 20598667. Excluded for wrong intervention.
3. Acharya UR, Mookiah MR, Koh JE, et al. Automated screening system for retinal health using bi-dimensional empirical mode decomposition and integrated index. *Comput Biol Med*. 2016;75:54-62. doi: 10.1016/j.compbimed.2016.04.015. PMID: 27253617. Excluded for results not usable or not fully reported.
4. Acharya UR, Mookiah MR, Koh JE, et al. Novel risk index for the identification of age-related macular degeneration using radon transform and DWT features. *Comput Biol Med*. 2016;73:131-40. doi: 10.1016/j.compbimed.2016.04.009. PMID: 27107676. Excluded for wrong intervention.
5. Age-Related Eye Disease Study Research Group. The age-related eye disease study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the age-related eye disease study report number 6. *Am J Ophthalmol*. 2001;132(5):668-81. doi: 10.1016/S0002-9394(01)01218-1. Excluded for ancillary publication not relevant to the current systematic review.
6. Agostini H, Mulyukov Z, Tsilimbaris M, et al. Comparison of the efficacy of brolocizumab with natural disease progression in wet AMD using clinical data from the phase III HAWK and HARRIER trials and dodelled placebo data. *Curr Eye Res*. 2020;1-4. doi: 10.1080/02713683.2020.1731832. PMID: 32065533. Excluded for wrong study design for key question.
7. Agron E, Mares J, Clemons TE, et al. Dietary nutrient intake and progression to late age-related macular degeneration in the Age-Related Eye Disease Studies 1 and 2. *Ophthalmology*. 2021;128(3):425-55. doi: 10.1016/j.ophtha.2020.08.018. PMID: 32858063. Excluded for ancillary publication not relevant to current systematic review.
8. Ahmed D, Stattin M, Graf A, et al. Detection of treatment-naive choroidal neovascularization in age-related macular degeneration by swept source optical coherence tomography angiography. *Retina*. 2018;38(11):2143-9. doi: 10.1097/IAE.0000000000001832. PMID: 28902095. Excluded for wrong population.
9. Akuffo KO, Beatty S, Peto T, et al. The impact of supplemental antioxidants on visual function in nonadvanced age-related macular degeneration: a head-to-head randomized clinical trial. *Invest Ophthalmol Vis Sci*. 2017;58(12):5347-60. doi: 10.1167/iovs.16-21192. PMID: 29053808. Excluded for wrong comparator.
10. Akuffo KO, Nolan JM, Howard AN, et al. Sustained supplementation and monitored response with differing carotenoid formulations in early age-related macular degeneration. *Eye*. 2015;29(7):902-12. doi: 10.1038/eye.2015.64. PMID: 25976647. Excluded for wrong comparator.
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12. Amin R, Saputra EB. Efficacy of oral glutathione addition in lutein supplementation on contrast sensitivity improvement in dry age-related macular degeneration: a randomized controlled trial. *Asian J Pharm Clin Res*. 2019;12(3):397-9. Excluded for wrong outcome.
13. Amlani A, Choi MY, Tarnopolsky M, et al. Anti-NT5c1A autoantibodies as biomarkers in inclusion body myositis. *Front Immunol*. 2019;10:745. doi: 10.3389/fimmu.2019.00745. PMID: 31024569. Excluded for wrong population.
14. Aslam TM, Zaki HR, Mahmood S, et al. Use of a neural net to model the impact of optical coherence tomography abnormalities on vision in age-related macular degeneration. *Am J Ophthalmol*. 2018;185:94-100. doi: 10.1016/j.ajo.2017.10.015. PMID: 29101008. Excluded for wrong outcome.
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Appendix A5. Excluded Studies

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17. Barikian A, Mahfoud Z, Abdulaal M, et al. Induction with intravitreal bevacizumab every two weeks in the management of neovascular age-related macular degeneration. *Am J Ophthalmol*. 2015;159(1):131-7. doi: 10.1016/j.ajo.2014.10.005. PMID: 25308787. Excluded for wrong comparator.
18. Bartlett H, Eperjesi F. A randomised controlled trial investigating the effect of nutritional supplementation on visual function in normal, and age-related macular disease affected eyes: design and methodology [ISRCTN78467674]. *Nutr J*. 2003;2:12. doi: 10.1186/1475-2891-2-12. PMID: 14594455. Excluded for study covered in an included systematic review.
19. Beatty S, Nolan JM, Muldrew KA, et al. Visual outcome after antioxidant supplementation. *Ophthalmology*. 2013;120(3):645. doi: 10.1016/j.ophtha.2012.09.013. PMID: 23714607. Excluded for wrong publication type.
20. Bell KJ, Hayen A, Glasziou P, et al. Early CRT monitoring using time-domain optical coherence tomography does not add to visual acuity for predicting visual loss in patients with central retinal vein occlusion treated with intravitreal ranibizumab: a secondary analysis of trial data. *Retina*. 2017;37(3):509-14. PMID: 27548351. Excluded for wrong intervention.
21. Bhandari S, Nguyen V, Arnold J, et al. Treatment outcomes of ranibizumab versus aflibercept for neovascular age-related macular degeneration: data from the Fight Retinal Blindness! Registry. *Ophthalmology*. 2020;127(3):369-76. doi: 10.1016/j.ophtha.2019.10.006. PMID: 31757494. Excluded for wrong study design for key question.
22. Bhisitkul RB, Desai SJ, Boyer DS, et al. Fellow eye comparisons for 7-year outcomes in ranibizumab-treated AMD subjects from ANCHOR, MARINA, and HORIZON (SEVEN-UP study). *Ophthalmology*. 2016;123(6):1269-77. doi: 10.1016/j.ophtha.2016.01.033. PMID: 26996339. Excluded for wrong comparator.
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26. Broadhead GK, Grigg JR, McCluskey P, et al. Saffron therapy for the treatment of mild/moderate age-related macular degeneration: a randomised clinical trial. *Graefes Arch Clin Exp Ophthalmol*. 2019;257(1):31-40. doi: 10.1007/s00417-018-4163-x. PMID: 30343354. Excluded for ancillary publication not relevant to current systematic review.
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31. Camp AS, Shane TS, Kang J, et al. Evaluating self-refraction and ready-made spectacles for treatment of uncorrected refractive error. *Ophthalmic Epidemiol.* 2018;25(5-6):392-8. doi: 10.1080/09286586.2018.1500615. PMID: 30118609. Excluded for wrong intervention.
32. Carrasco J, Pietsch GA, Nicolas MP, et al. Real-world effectiveness and real-world cost-effectiveness of intravitreal aflibercept and intravitreal ranibizumab in neovascular age-related macular degeneration: systematic review and meta-analysis of real-world studies. *Adv Ther.* 2020;37(1):300-15. doi: 10.1007/s12325-019-01147-6. PMID: 31728825. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.
33. Castillo MM, Mowatt G, Elders A, et al. Optical coherence tomography for the monitoring of neovascular age-related macular degeneration: a systematic review. *Ophthalmology.* 2015;122(2):399-406. doi: 10.1016/j.ophtha.2014.07.055. PMID: 25444343. Excluded for wrong population.
34. Chakravarthy U, Adamis AP, Cunningham ET, Jr., et al. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology.* 2006;113(9):1508.e1-25. doi: 10.1016/j.ophtha.2006.02.064. PMID: 16828500. Excluded for wrong intervention.
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36. Chamard C, Lacombe S, Navarre S, et al. Is current age related macular degeneration self-monitoring a good tool for detecting exudative recurrence? *J Fr Ophtalmol.* 2019;42(10):1049-55. doi: 10.1016/j.jfo.2019.02.017. PMID: 31727329. Excluded for wrong study design for key question.
37. Chandrasekaran N, Harlow S, Moroi S, et al. Visual impairment at baseline is associated with future poor physical functioning among middle-aged women: the Study of Women's Health Across the Nation, Michigan Site. *Maturitas.* 2017;96:33-8. doi: 10.1016/j.maturitas.2016.11.009. PMID: 28041592. Excluded for wrong intervention.
38. Chang AA, Broadhead GK, Hong T, et al. Intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration: 12-month safety and efficacy outcomes. *Ophthalmic Res.* 2015;55(2):84-90. doi: 10.1159/000440886. PMID: 26637166. Excluded for wrong population.
39. Chen JS, Adelman RA. Hyperacuity exam screens for choroidal neovascularization in age-related macular degeneration on a mobile device. *Ophthalmic Surg Lasers Imaging Retina.* 2016;47(8):708-15. doi: 10.3928/23258160-20160808-03. PMID: 27548447. Excluded for wrong outcome.
40. Cheung CMG, Yanagi Y, Akiba M, et al. Improved detection and diagnosis of polypoidal choroidal vasculopathy using a combination of optical coherence tomography and optical coherence tomography angiography. *Retina.* 2019;39(9):1655-63. doi: 10.1097/IAE.0000000000002228. PMID: 29927796. Excluded for wrong intervention.
41. Chew EY, Clemons TE, Agron E, et al. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. *JAMA Ophthalmol.* 2014;132(3):272-7. doi: 10.1001/jamaophthalmol.2013.6636. PMID: 24385141. Excluded for ancillary publication not relevant to current systematic review.
42. Chew EY, Clemons TE, Sangiovanni JP, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. *JAMA Ophthalmol.* 2014;132(2):142-9. doi: 10.1001/jamaophthalmol.2013.7376. PMID: 24310343. Excluded for ancillary publication not relevant to current systematic review.
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44. Christen WG, Glynn RJ, Chew EY, et al. Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study. *Arch Intern Med.* 2009;169(4):335-41. doi: 10.1001/archinternmed.2008.574. PMID: 19237716. Excluded for wrong population.
45. Christen WG, Glynn RJ, Chew EY, et al. Folic acid, vitamin B6, and vitamin B12 in combination and age-related cataract in a randomized trial of women. *Ophthalmic Epidemiol.* 2016;23(1):32-9. doi: 10.3109/09286586.2015.1130845. PMID: 26786311. Excluded for wrong outcome.
46. Clarke EL, Evans JR, Smeeth L. Community screening for visual impairment in older people. *Cochrane Database Syst Rev.* 2018;2:CD001054. doi: 10.1002/14651858.CD001054.pub3. PMID: 29460275. Excluded for systematic review or meta-analysis used as a source document only to identify individual studies.
47. Clemens CR, Wolf A, Alten F, et al. Response of vascular pigment epithelium detachment due to age-related macular degeneration to monthly treatment with ranibizumab: the prospective, multicentre RECOVER study. *Acta Ophthalmol.* 2017;95(7):683-9. doi: 10.1111/aos.13359. PMID: 28084038. Excluded for wrong population.
48. Conlin PR, Asefzadeh B, Pasquale LR, et al. Accuracy of a technology-assisted eye exam in evaluation of referable diabetic retinopathy and concomitant ocular diseases. *Br J Ophthalmol.* 2015;99(12):1622-7. doi: 10.1136/bjophthalmol-2014-306536. PMID: 25995299. Excluded for wrong study design for key question.
49. Csaky KG, Dugel PU, Pierce AJ, et al. Clinical evaluation of pazopanib eye drops versus ranibizumab intravitreal injections in subjects with neovascular age-related macular degeneration. *Ophthalmology.* 2015;122(3):579-88. doi: 10.1016/j.ophtha.2014.09.036. PMID: 25432081. Excluded for wrong intervention.
50. Cui C, Lu H. Clinical observations on the use of new anti-VEGF drug, conbercept, in age-related macular degeneration therapy: a meta-analysis. *Clin Interv Aging.* 2018;13:51-62. doi: 10.2147/CIA.S151225. PMID: 29343949. Excluded for wrong intervention.
51. Cui QN, Gray IN, Yu Y, et al. Repeated intravitreal injections of antivascular endothelial growth factors and risk of intraocular pressure medication use. *Graefes Arch Clin Exp Ophthalmol.* 2019;257(9):1931-9. doi: 10.1007/s00417-019-04362-7. PMID: 31152311. Excluded for wrong study design for key question.
52. Cumberland PM, Chianca A, Rahi JS. Accuracy and utility of self-report of refractive error. *JAMA Ophthalmol.* 2016;134(7):794-801. PMID: 27197004. Excluded for wrong intervention.
53. Cumming RG, Ivers R, Clemson L, et al. Improving vision to prevent falls in frail older people: a randomized trial. *J Am Geriatr Soc.* 2007;55(2):175-81. Excluded for wrong screener.
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138. Lee CS, Baughman DM, Lee AY. Deep learning is effective for the classification of OCT images of normal versus age-related macular degeneration. *Ophthalmol Retina*. 2017;1(4):322-7. doi: 10.1016/j.oret.2016.12.009. PMID: 30693348. Excluded for wrong intervention.
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Appendix A6. US Preventive Services Task Force Quality Criteria

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of ratings based on above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
 - For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
 - For cohort studies: consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs

Definition of ratings based on above criteria:

Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study (followup greater than or equal to 80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: generally comparable groups are assembled initially,

Appendix A6. US Preventive Services Task Force Quality Criteria

but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.

Poor: Studies are graded "poor" if any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (greater than 100) of broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has a fatal flaw, such as: uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients.

Internet Citation: *Appendix VI. Criteria for Assessing Internal Validity of Individual Studies*. U.S. Preventive Services Task Force. July 2017. <https://www.uspreventiveservicestaskforce.org/uspstf/procedure-manual/procedure-manual-appendix-vi-criteria-assessing-internal-validity-individual-studies>

Appendix A7. Expert Reviewers of the Draft Report

- ❖ April Maa, MD, Emory University School of Medicine, Emory Eye Center; Atlanta VA Medical Center
- ❖ Nancy Weintraub, MD, David Geffen School of Medicine at University of California at Los Angeles
- ❖ Jennifer Evans, PhD, MSc, London School of Hygiene and Tropical Medicine
- ❖ Centers for Disease Control and Prevention representatives
- ❖ One undisclosed reviewer

Note: Reviewers provided comments on a prior version of the draft report and may or may not agree with the report findings.

Appendix B Table 1. Trials of Vision Screening

Author, year	Study design	Country	Setting	Ns	Duration of followup	Inclusion criteria	Baseline population	Baseline vision parameters	Screening tools used
Eekhof, 2000 <i>From prior report</i>	Cluster RCT	The Netherlands	12 general practices	Included 1,470 Analyzed 1,121	2 years	Aged 70+ years Excluded those too ill, suffering from dementia, or otherwise not able to participate	Mean age: 81 years % female: 64% Race/ethnicity: NR	NR	Validated diagnostic tests: Assessment of difficulty in recognizing a face at 4 m and/or reading normal letters in a newspaper, and/or impaired vision with both by Snellen eye chart or not being able to read normal newspaper letters at 25 cm distance Vision was measured with the glasses usually worn
Moore, 1997 <i>From prior report</i>	Cluster RCT	United States	26 community-based office practices (family physicians or internists); 36 agreed to participate	Approached 316 Analyzed for detection 261 Analyzed at 6 months for improvement 230	6 months	Aged 70+ years, English speaking, not acutely or terminally ill, and able to answer questions	Mean age: 76 years % female: 62% Race/ethnicity: NR	NR	Question, "Do you have difficulty driving or watching television or reading or doing any of your daily activities because of your eyesight (even while wearing glasses)?", followed by Snellen eye chart if positive

Appendix B Table 1. Trials of Vision Screening

Author, year	Study design	Country	Setting	Ns	Duration of followup	Inclusion criteria	Baseline population	Baseline vision parameters	Screening tools used
Smeeth, 2003 MRC Trial <i>From prior report</i>	Cluster RCT	United Kingdom	20 general practices	Randomized 4,340 Received intervention 3,249 Completed outcome at followup 1,807	3-5 years	Random sample from MRC trial, aged 75+ years Excluded residents in a long stay hospital or nursing home or were terminally ill	Mean age: 80 years % female: 62% Race/ethnicity: NR ≥1 fall in home during previous 6 months: 20% vs. 18% Taking ≥5 drugs regularly: 19% vs. 18%	Reported difficulty seeing newsprint: 8% vs. 10%	Detailed health assessment: VA measured using Glasgow acuity eye chart (Snellen equivalent provided in results), and pinhole testing if VA less than 6/18 in either eye; referral to ophthalmologist when appropriate Brief health assessment: Covered all areas specified in the GP contract, including a question about difficulty seeing, but did not include measurement of VA. Those with a specified range and level of problems were eligible to have a detailed assessment Note: reporting difficulty seeing was not on its own sufficient to lead to a detailed assessment

Appendix B Table 1. Trials of Vision Screening

Author, year	Study design	Country	Setting	Ns	Duration of followup	Inclusion criteria	Baseline population	Baseline vision parameters	Screening tools used
Tay, 2006 ACCS Added Jee 2004	RCT	Australia	1 geriatric day hospital or home visit	Randomized 206 Participated at baseline 91% (188/206) Retained at 1 year followup 59% (121/206)	1 year	Aged 65+ years, English-speaking, absence of profound dementia, assessed for aged care provision at Westmead Hospital	N=188 Mean age: 83 years % female: 62% Race/ethnicity: NR ≥ 1 fall in home during previous 6 months: 58%	N=96 (reported for those in vision intervention arm only) 31% (30/96) bilateral visual impairment, 29% (28/96) unilateral visual impairment, 88% (84/96) with VA <6/6 and of those 17% (14/84) had under-corrected refractive error 69% (66/96) recommended to see eye care professional	logMAR chart for presenting VA for distance (with glasses, if worn) using letters read correctly using ETDRS-Fast protocol Binocular near vision and visual field using confrontation method Self report questions: Did you notice any deterioration in one or both eyes? Are you able to recognize a friend across the street? Can you read the ordinary print in the newspaper reasonably well, with or without glasses?

Appendix B Table 1. Trials of Vision Screening

Author, Year	Screeener	Intervention (Ns)	Results	Harms	Quality
Eekhof, 2000 <i>From prior report</i>	GP	A. Vision screening (n=576) B. Delayed screening (n=545) Note: part of larger intervention to also assess hearing, urinary incontinence, and mobility	A vs. B Vision disorder detected: 49% (95% CI 43% to 54%) vs. NR Visual disorder in 2nd year: 51% (95% CI 45% to 58%) vs. 47% (95% CI 42% to 52%); p=0.68	NR	Fair
Moore, 1997 <i>From prior report</i>	Office staff	A. Vision screening, coupled with clinical summaries (n=112) B. Usual care (n=149) Note: part of a larger intervention to also assess malnutrition, hearing, cognitive impairment, depression, etc.	A vs. B Vision problem detected: 20% vs. 19%, p=0.84 Improvement in vision at 6 months: 20% (20/99) vs. 24% (31/131); RR 0.85 (95% CI 0.52 to 1.40)	NR	Fair
Smeeth, 2003 MRC Trial <i>From prior report</i>	Trained nurse	A. Universal screening = brief health assessment plus detailed health assessment, latter of which included measurement of VA (n=1,565) B. Targeted screening = brief health assessment (n=1,684, 120 of which had a detailed assessment due to severity of problems, though 150 were eligible)	A vs. B Found to have VA <6/18 (20/60) in either eye: 29% (451/1565) vs. 3.1% (53/1684) Eligible for referral to ophthalmologist: 14% (220/1565) vs. 1.7% (29/1684) Eligible for referral to optician: 5% (79/1565) vs. 0.4% (8/1684) At followup: VA <6/18 (20/60) in either eye at 3 years: 37% (307/829) vs. 35% (339/978), RR 1.07 (95% CI 0.84 to 1.36) VA <6/18 binocular vision: 14% (114/817) vs. 17% (160/962), RR 0.84 (95% CI 0.64 to 1.10) VA <6/12 in either eye: 59% (486/829) vs. 60% (584/978), RR 0.98 (95% CI 0.82 to 1.17) VA <6/12 binocular vision: 31% (256/817) vs. 37% (351/962), RR 0.86 (95% CI 0.65 to 1.13) NEI-VFQ mean composite score (scale 0 to 100; higher score = better QoL): 86.0 vs. 85.6; MD 0.4 (95% CI -1.7 to 2.5)	NR	Fair
Tay, 2006 ACCS <i>Added Jee 2004</i>	Study investigator or orthoptist	Routine aged care assessment and interview using a standardized questionnaire, plus: A. Vision screening* (n=96) B. No vision screening* (n=92) Note: Vision screening can include referral to an eye care professional * -Half of these also received hearing screening	A vs B Mean VA: 39 letters vs. 35 letters, p=0.25 Bilateral visual impairment: 35% vs. 47%, p=0.17 Regardless of the intervention groups, 90/121 (those retained at followup) reported seeing an eye care professional within the past year	NR	Fair

Abbreviations: ACCS = Aged Care Client pilot Study; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; GP = general practitioner; logMAR = logarithmic minimum angle of resolution; MRC = Medical Research Council; NEI-VFQ = National Eye Institute Vision Function Questionnaire; NR = not reported; QoL = quality of life; RCT = randomized controlled trial; RR = relative risk; VA=visual acuity.

Appendix B Table 2. Trials of Vision Screening, Quality Assessment

Study, year	Random assignment	Allocation concealment	Groups similar at baseline	Eligibility criteria specified	Blinding: outcome assessors or data analysts	Intention-to-treat analysis	Reporting of attrition, contamination, etc.	Differential loss to followup or overall high loss to followup	Appropriate analysis including cluster correlation	Funding source	Quality
Eekhof 2000 <i>From prior report</i>	Yes	NA (cluster)	Yes	Yes	Unclear	No	Yes	21% and 26%	No	Unclear	Fair
Moore 1997 <i>From prior report</i>	Yes	NA (cluster)	Yes	Yes	Unclear	No	Yes	12% and 12%	No	Robert Wood Johnson Clinical Scholars Program; National Institute on Aging Geriatric Academic Program	Fair
Smeeth 2003 <i>From prior report</i>	Yes	NA (cluster)	Yes	Yes	No	No	Yes	27% vs. 23% assessments Longer term outcomes 61% and 55%	Yes	Medical Research Council/ United Kingdom Department of Health	Fair
Tay 2006 <i>Added</i>	Yes	Unclear	Unclear	Yes	Unclear	No	Yes	Unclear 41% attrition overall	NA	University of Sydney, Ophthalmic Research Institute of Australia, Westmead Millennium foundation Research Scholarship Stipend Enhancement Grant	Fair

Abbreviation: NA = not applicable.

Appendix B Table 3. Diagnostic Accuracy of Vision Screening Tests, Study Characteristics

Study, year	Study design	Target vision condition	Screening test	Reference standard	Setting country	Screeener	N	Baseline population	Baseline vision parameters	Quality
Ariyasu, 1996 <i>From prior report</i>	Cross-sectional, presenting consecutively, prospective	Visually disabling or vision-threatening eye conditions	Amsler grid Vistech hand-held 9-item contrast sensitivity cards Hand-held pocket eyechart Projected Snellen chart	Ophthalmologic examination	General eye clinic (intended for primary care) United States	Unclear; intended for primary care	317 people	Mean age: 44 years (≥ 60 years 21% [68/317]) % female 60% Race/ethnicity: 77% Hispanic, 10% black, 7.6% white, 4.4% Asian	43% refractive error, 16% cataract, 4.1% macular degeneration, 7.3% glaucoma, 18% normal	Fair
Arora 2014 <i>New</i>	Cross-sectional	VA	iPod application to rapidly measure approximate VA (randomized ETDRS letters at the Snellen equivalent of 20/40 and 20/200 each)	Standard ETDRS VA testing	Unclear - selected from tertiary referral glaucoma and retina practices United States	Unclear	104 people	Mean age: 67 years Female sex: 63% Race: 69% white, 25% black, 3% Hispanic, 3% Asian or Pacific Islander	ETDRS VA (logMAR), mean 0.48 ETDRS VA: 44% $\geq 20/40$ (good vision), 43% $< 20/40$ to $\geq 20/200$ (decreased vision), 13% $< 20/200$ (poor vision) Impaired VA: 56%	Fair
Ivers, 2001 Blue Mountains Eye Study <i>From prior report</i>	Cross-sectional, population-based	A: Nuclear cataract B: Early AMD C: Any eye disease	Presenting distance VA (logMAR chart) Pinhole distance VA Presenting reading acuity (with current reading glasses)	Ophthalmologic examination	Hospital clinic Australia	Unclear	3654 people	49 years or older	3.9% posterior subcapsular cataract, 19.1% cortical cataract, 47.0% nuclear cataract, 4.5% early AMD, 4.5% refractive error, 34.50% any vision condition	Fair
Jessa, 2012 Study 1 <i>From prior report</i>	Cross-sectional	Refractive error, cataracts, AMD	6-item CVS - to determine which tests were most useful Included: symptoms and history, near VA, visual field test, fixation disparity,	Gold standard eye exam	Community day center, optometrist offices, GP surgery center United Kingdom	Computer	180 people	Mean age: 77 years 54% female	Cataract: 31.7% Significant uncorrected refractive error: 39.4% Correctable visual loss: 58.3% Significant macular	Fair

Appendix B Table 3. Diagnostic Accuracy of Vision Screening Tests, Study Characteristics

Study, year	Study design	Target vision condition	Screening test	Reference standard	Setting country	Screeener	N	Baseline population	Baseline vision parameters	Quality
			stereoacuity, high contrast distance VA, low contrast distance VA						degeneration: 28.9% Spectacles: 10% no spectacles, 46.6% multifocal, 23.9% distance vision, 38.3% near vision	
Jessa, 2012 Study 2 <i>From prior report</i>	Cross-sectional	Refractive error, cataracts, AMD	Modified 4-item CVS and FVS For CVS, same as above, but omitted fixation disparity and stereoacuity tests	Gold standard eye exam	Community day center, optometrist offices, GP surgery center United Kingdom	Computer	200 people	Mean age: 77 years 69% female	Cataract: 30.7% Significant uncorrected refractive error: 30% Correctable visual loss: 51% Significant macular degeneration: 22.5% Spectacles: 14.5% no spectacles, 44.5% multifocal, 22.5% distance vision, 31.5% near vision	Fair
McMurdo, 1988 <i>From prior report</i>	Cross-sectional	Cataract, AMD	Positive finding on physical examination	Ophthalmologist examination	Geriatric day hospital Australia	Geriatrician	50 people	64 to 97 years	Unsuspected, severe visual impairment: 32% Previously undiagnosed cataract: 18% Previously undiagnosed AMD: 8% Previously undiagnosed glaucoma: 6%	Fair

Appendix B Table 3. Diagnostic Accuracy of Vision Screening Tests, Study Characteristics

Study, year	Study design	Target vision condition	Screening test	Reference standard	Setting country	Screeener	N	Baseline population	Baseline vision parameters	Quality
Swanson, 2009 <i>From prior report</i>	Cross-sectional	Any eye disease	MDS 2.0 Vision Patterns questions from medical record	ETDRS chart (distance VA) Lighthouse Near VA Chart (near VA)	17 nursing homes United States	Trained research staff	371 people	Mean age: 80.7 years Female sex: 80.6% Race: 73.3% white, 26.4% black, 0.3% Hispanic Mean MMSE: 20.9	Impaired VA, MDS: 40.6% (151/371) Near VA, better eye: 0.56 Near VA, worse eye: 0.81 Distance VA, better eye: 0.43 Distance VA, worse eye: 0.64 Contrast sensitivity, better eye: 1.14 Contrast sensitivity, worse eye: 0.83	Fair
Woods, 1998 (Mitchell 1993) <i>From prior report</i>	Cross-sectional, retrospective analysis	Any ocular disease, excluding refractive error	Snellen for Presenting distance VA ≤20/30 Near VA ≤20/30 Arden plates for contrast sensitivity	Ophthalmologic examination	Primary care Australia	GPs	2522 confirmed by ophthalmologist 283 people total	50 years or older	Those confirmed by expert (2522) stratified by 50 to 64 years vs. >64 years: AMD: 12% vs. 23% Cataract: 4.9% vs. 27.2% Any eye disease: 37% vs. 73%	Fair

Abbreviations: AMD = age-related macular degeneration; CVS = computerized vision screener; ETDRS = Early Treatment Diabetic Retinopathic Study; FVS = flip-chart vision screener; GP = general practitioner; logMAR = logarithmic minimum angle of resolution; MDS = minimum data set; MMSE = Mini-Metal State Examination; VA = visual acuity.

Appendix B Table 4. Diagnostic Accuracy of Vision Screening Tests, Results

Study, year	Test	Reference standard	Target vision condition	Screening test detail	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	TP	FN	TN	FP
Ariyasu, 1996 <i>From prior report</i>	Amsler grid	Ophthalmologic examination	Any ocular disease, excluding refractive error	Amsler grid	0.20 (0.14-0.27)	0.88 (0.80-0.94)	1.65 (0.90-3.06)	0.91 (0.82-1.01)	32	126	86	12
Ariyasu, 1996 <i>From prior report</i>	VA testing	Ophthalmologic examination	Any ocular disease, excluding refractive error	Near VA $\leq 20/30$	0.83 (0.75-0.89)	0.32 (0.23-0.44)	1.23 (1.04-1.46)	0.52 (0.32-0.86)	107	22	27	56
Ariyasu, 1996 <i>From prior report</i>	VA testing	Ophthalmologic examination	Any ocular disease, excluding refractive error	Near VA $\leq 20/40$	0.76 (0.68-0.83)	0.49 (0.38-0.61)	1.50 (1.19-1.90)	0.49 (0.33-0.71)	98	31	41	42
Ariyasu, 1996 <i>From prior report</i>	VA testing	Ophthalmologic examination	Any ocular disease, excluding refractive error	Near VA $\leq 20/60$	0.60 (0.52-0.69)	0.64 (0.53-0.74)	1.67 (1.22-2.30)	0.62 (0.47-0.81)	78	51	53	30
Ariyasu, 1996 <i>From prior report</i>	VA testing	Ophthalmologic examination	Any ocular disease, excluding refractive error	Presenting distance VA $\leq 20/30$	0.75 (0.69-0.81)	0.51 (0.42-0.61)	1.54 (1.26-1.90)	0.48 (0.36-0.65)	151	50	58	55
Ariyasu, 1996 <i>From prior report</i>	VA testing	Ophthalmologic examination	Any ocular disease, excluding refractive error	Presenting distance VA $\leq 20/40$	0.68 (0.61-0.74)	0.67 (0.58-0.76)	2.08 (1.57-2.76)	0.47 (0.37-0.60)	137	64	76	37
Ariyasu, 1996 <i>From prior report</i>	VA testing	Ophthalmologic examination	Any ocular disease, excluding refractive error	Presenting distance VA $\leq 20/60$	0.53 (0.46-0.60)	0.86 (0.78-0.92)	3.76 (2.34-6.03)	0.54 (0.46-0.64)	107	94	97	16
Arora, 2014 <i>New</i>	VA testing with mobile application	ETDRS VA testing	VA $\leq 20/40$	4 of 4 images incorrect	0.98 (0.91-1.00)	0.94 (0.82-0.99)	15.07 (5.04-45.03)	0.02 (0.00-0.13)	57	1	43	3

Appendix B Table 4. Diagnostic Accuracy of Vision Screening Tests, Results

Study, year	Test	Reference standard	Target vision condition	Screening test detail	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	TP	FN	TN	FP
Arora, 2014 <i>New</i>	VA testing with mobile application	ETDRS VA testing	VA <20/200	4 of 4 images incorrect	0.92 (0.64-1.00)	0.92 (0.85-0.97)	12.00 (5.79-24.87)	0.08 (0.01-0.55)	12	1	84	7
Ivers, 2001 <i>From prior report</i>	VA testing	Ophthalmologic examination	A: Nuclear cataract B: Early AMD C: Any eye disease	Pinhole distance acuity ≤20/30	A: 0.31 (0.28-0.34) B: 0.45 (0.37-0.53) C: 0.34 (0.31-0.37)	A: 0.89 (0.87-0.91) B: 0.79 (0.78-0.80) C: 0.86 (0.85-0.87)	A: 2.83 (2.35-3.40) B: 2.16 (1.80-2.59) C: 2.43 (2.14-2.76)	A: 0.77 (0.74-0.81) B: 0.69 (0.60-0.80) C: 0.77 (0.74-0.80)	334 72 429	743 87 832	1080 2672 2058	133 710 335
Ivers, 2001 <i>From prior report</i>	VA testing	Ophthalmologic examination	A: Nuclear cataract B: Early AMD C: Any eye disease	Pinhole distance acuity ≤20/40	A: 0.13 (0.11-0.15) B: 0.21 (0.15-0.28) C: 0.15 (0.13-0.17)	A: 0.98 (0.97-0.99) B: 0.92 (0.91-0.93) C: 0.96 (0.95-0.97)	A: 6.57 (4.29-10.05) B: 2.59 (1.87-3.59) C: 3.74 (2.95-4.73)	A: 0.89 (0.87-0.91) B: 0.86 (0.80-0.93) C: 0.89 (0.86-0.91)	140 33 189	937 126 1072	1189 3111 2297	24 271 96
Ivers, 2001 <i>From prior report</i>	VA testing	Ophthalmologic examination	A: Nuclear cataract B: Early AMD C: Any eye disease	Pinhole distance acuity ≤20/60	A: 0.08 (0.06-0.10) B: 0.10 (0.06-0.16) C: 0.09 (0.08-0.11)	A: 0.99 (0.98-1.00) B: 0.95 (0.94-0.96) C: 0.97 (0.96-0.98)	A: 8.07 (4.44-14.68) B: 2.01 (1.24-3.28) C: 3.00 (2.25-4.00)	A: 0.93 (0.91-0.95) B: 0.95 (0.90-1.00) C: 0.94 (0.92-0.96)	86 16 114	991 143 1147	1201 3213 2321	12 169 72
Ivers, 2001 <i>From prior report</i>	VA testing	Ophthalmologic examination	A: Nuclear cataract B: Early AMD C: Any eye disease	Presenting distance VA ≤20/30	A: 0.44 (0.41-0.47) B: 0.56 (0.48-0.64) C: 0.47 (0.44-0.50)	A: 0.77 (0.75-0.79) B: 0.66 (0.64-0.68) C: 0.74 (0.72-0.76)	A: 1.91 (1.69-2.16) B: 1.65 (1.42-1.90) C: 1.81 (1.65-1.98)	A: 0.73 (0.68-0.77) B: 0.67 (0.56-0.80) C: 0.72 (0.68-0.76)	474 89 593	603 70 668	934 2232 1771	279 1150 622
Ivers, 2001 <i>From prior report</i>	VA testing	Ophthalmologic examination	A: Nuclear cataract B: Early AMD C: Any eye disease	Presenting distance VA ≤20/40	A: 0.25 (0.22-0.28) B: 0.34 (0.27-0.42) C: 0.27 (0.24-0.30)	A: 0.90 (0.88-0.92) B: 0.82 (0.81-0.83) C: 0.87 (0.86-0.88)	A: 2.50 (2.05-3.05) B: 1.89 (1.50-2.37) C: 2.08 (1.81-2.39)	A: 0.83 (0.80-0.87) B: 0.81 (0.72-0.90) C: 0.84 (0.81-0.87)	269 54 341	808 105 920	1092 2773 2082	121 609 311
Ivers, 2001 <i>From prior report</i>	VA testing	Ophthalmologic examination	A: Nuclear cataract B: Early AMD C: Any eye disease	Presenting distance VA ≤20/60	A: 0.13 (0.11-0.15) B: 0.13 (0.08-0.20)	A: 0.96 (0.95-0.97) B: 0.92 (0.91-0.93)	A: 3.28 (2.39-4.51) B: 1.65 (1.09-2.49)	A: 0.91 (0.88-0.93) B: 0.94 (0.89-1.00)	140 211 77	9371 3810 84	1165 3111 2249	48271 144

Appendix B Table 4. Diagnostic Accuracy of Vision Screening Tests, Results

Study, year	Test	Reference standard	Target vision condition	Screening test detail	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	TP	FN	TN	FP
			Any eye disease		C: 0.14 (0.12-0.16)	C: 0.94 (0.93-0.95)	C: 2.33 (1.89-2.88)	C: 0.91 (0.89-0.94)				
Ivers, 2001 <i>From prior report</i>	VA testing	Ophthalmologic examination	A: Nuclear cataract B: Early AMD C: Any eye disease	Reading acuity ≤20/30	A: 0.97 (0.96-0.98) B: 0.99 (0.96-1.00) C: 0.98 (0.97-0.99)	A: 0.03 (0.02-0.04) B: 0.03 (0.03-0.04) C: 0.03 (0.02-0.04)	A: 1.00 (0.99-1.01) B: 1.02 (1.00-1.04) C: 1.01 (1.00-1.02)	A: 1.00 (0.63-1.60) B: 0.42 (0.10-1.68) C: 0.66 (0.42-1.03)	104 5 157 123 6	32 2 25	36 102 72	1177 3280 2321
Ivers, 2001 <i>From prior report</i>	VA testing	Ophthalmologic examination	A: Nuclear cataract B: Early AMD C: Any eye disease	Reading acuity ≤20/40	A: 0.88 (0.86-0.90) B: 0.95 (0.90-0.98) C: 0.89 (0.87-0.91)	A: 0.20 (0.18-0.22) B: 0.16 (0.15-0.17) C: 0.18 (0.17-0.20)	A: 1.10 (1.06-1.14) B: 1.13 (1.09-1.18) C: 1.09 (1.06-1.12)	A: 0.60 (0.49-0.73) B: 0.31 (0.16-0.62) C: 0.61 (0.51-0.72)	948 151 112 2	129 8 139	243 541 436	970 2841 1957
Ivers, 2001 <i>From prior report</i>	VA testing	Ophthalmologic examination	A: Nuclear cataract B: Early AMD C: Any eye disease	Reading acuity ≤20/50	A: 0.57 (0.54-0.60) B: 0.70 (0.62-0.77) C: 0.59 (0.56-0.62)	A: 0.59 (0.56-0.62) B: 0.53 (0.51-0.55) C: 0.59 (0.57-0.61)	A: 1.39 (1.28-1.52) B: 1.49 (1.33-1.66) C: 1.44 (1.35-1.54)	A: 0.73 (0.67-0.79) B: 0.57 (0.45-0.72) C: 0.69 (0.65-0.75)	614 111 744	463 48 517	716 1793 1412	497 1589 981
Jessa, 2012 Study 1 <i>From prior report</i>	CVS	Gold standard eye exam	Cataract	High-contrast (VA >0.19 logMAR)	0.86 (0.74-0.94)	0.51 (0.42-0.60)	1.76 (1.43-2.17)	0.27 (0.14-0.53)	49	8	63	60
Jessa, 2012 Study 1 <i>From prior report</i>	CVS	Gold standard eye exam	Refractive error	High-contrast (VA >0.19 logMAR)	0.77 (0.66-0.87)	0.54 (0.44-0.64)	1.69 (1.33-2.15)	0.42 (0.26-0.66)	55	16	59	50
Jessa, 2012 Study 1 <i>From prior report</i>	CVS	Gold standard eye exam	Correctable visual loss	High-contrast (VA >0.19 logMAR)	0.79 (0.70-0.87)	0.60 (0.48-0.71)	1.98 (1.47-2.65)	0.35 (0.23-0.53)	83	22	45	30
Jessa, 2012 Study 1 <i>From prior report</i>	CVS	Gold standard eye exam	AMD	High-contrast (VA >0.19 logMAR)	0.75 (0.61-0.86)	0.50 (0.41-0.59)	1.50 (1.19-1.89)	0.50 (0.30-0.83)	39	13	64	64

Appendix B Table 4. Diagnostic Accuracy of Vision Screening Tests, Results

Study, year	Test	Reference standard	Target vision condition	Screening test detail	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	TP	FN	TN	FP
Jessa, 2012 Study 1 <i>From prior report</i>	CVS	Gold standard eye exam	Cataract	Low-contrast (VA >0.39 logMAR)	0.79 (0.66-0.89)	0.55 (0.46-0.64)	1.77 (1.39-2.24)	0.38 (0.22-0.65)	45	12	68	55
Jessa, 2012 Study 1 <i>From prior report</i>	CVS	Gold standard eye exam	Refractive error	Low-contrast (VA >0.39 logMAR)	0.69 (0.57-0.80)	0.55 (0.45-0.65)	1.54 (1.18-1.99)	0.56 (0.38-0.83)	49	22	60	49
Jessa, 2012 Study 1 <i>From prior report</i>	CVS	Gold standard eye exam	Correctable visual loss	Low-contrast (VA >0.39 logMAR)	0.67 (0.57-0.76)	0.59 (0.47-0.70)	1.61 (1.19-2.18)	0.57 (0.41-0.79)	70	35	44	31
Jessa, 2012 Study 1 <i>From prior report</i>	CVS	Gold standard eye exam	AMD	Low-contrast (VA >0.39 logMAR)	0.75 (0.61-0.86)	0.56 (0.47-0.65)	1.71 (1.33-2.20)	0.44 (0.27-0.73)	39	13	72	56
Jessa, 2012 Study 2 <i>From prior report</i>	CVS	Gold standard eye exam	Cataract	High-contrast (VA >0.19 logMAR)	0.64 (0.51-0.76)	0.60 (0.51-0.68)	1.59 (1.20-2.09)	0.60 (0.42-0.87)	39	22	83	56
Jessa, 2012 Study 2 <i>From prior report</i>	CVS	Gold standard eye exam	Refractive error	High-contrast (VA >0.19 logMAR)	0.73 (0.60-0.84)	0.61 (0.52-0.69)	1.87 (1.44-2.41)	0.44 (0.28-0.68)	44	16	85	55
Jessa, 2012 Study 2 <i>From prior report</i>	CVS	Gold standard eye exam	Correctable visual loss	High-contrast (VA >0.19 logMAR)	0.65 (0.55-0.74)	0.65 (0.55-0.75)	1.87 (1.37-2.54)	0.54 (0.40-0.73)	66	36	64	34
Jessa, 2012 Study 2 <i>From prior report</i>	CVS	Gold standard eye exam	AMD	High-contrast (VA >0.19 logMAR)	0.62 (0.47-0.76)	0.58 (0.50-0.66)	1.48 (1.11-1.99)	0.65 (0.44-0.97)	28	17	90	65

Appendix B Table 4. Diagnostic Accuracy of Vision Screening Tests, Results

Study, year	Test	Reference standard	Target vision condition	Screening test detail	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	TP	FN	TN	FP
Jessa, 2012 Study 2 <i>From prior report</i>	CVS	Gold standard eye exam	Cataract	Low-contrast (VA>0.39 logMAR)	0.64 (0.51-0.75)	0.65 (0.56-0.73)	1.81 (1.35-2.43)	0.56 (0.39-0.80)	39	22	90	49
Jessa, 2012 Study 2 <i>From prior report</i>	CVS	Gold standard eye exam	Refractive error	Low-contrast (VA >0.39 logMAR)	0.70 (0.57-0.81)	0.65 (0.57-0.73)	2.00 (1.51-2.65)	0.46 (0.31-0.69)	42	18	91	49
Jessa, 2012 Study 2 <i>From prior report</i>	CVS	Gold standard eye exam	Correctable visual loss	Low-contrast (VA >0.39 logMAR)	0.64 (0.54-0.73)	0.70 (0.60-0.79)	2.15 (1.53-3.02)	0.52 (0.39-0.69)	65	37	69	29
Jessa, 2012 Study 2 <i>From prior report</i>	CVS	Gold standard eye exam	AMD	Low-contrast (VA >0.39 LogMAR)	0.67 (0.51-0.80)	0.64 (0.56-0.71)	1.85 (1.38-2.48)	0.52 (0.34-0.80)	30	15	99	56
Jessa, 2012 Study 2 <i>From prior report</i>	CVS Optimal	Gold standard eye exam	SAIEC	High contrast VA (>0.19 logMAR) or low contrast VA (>0.39 logMAR) or near VA (threshold unclear)	0.80 (0.72-0.86)	0.67 (0.56-0.76)	2.42 (CI not calculable)	0.30 (CI not calculable)	NR	NR	NR	NR
Jessa, 2012 Study 2 <i>From prior report</i>	CVS Optimal	Gold standard eye exam	SAIEC	High-contrast VA (>0.19 logMAR) or near VA (threshold unclear)	0.80 (0.72-0.86)	0.68 (0.57-0.77)	2.50 (CI not calculable)	0.29 (CI not calculable)	NR	NR	NR	NR

Appendix B Table 4. Diagnostic Accuracy of Vision Screening Tests, Results

Study, year	Test	Reference standard	Target vision condition	Screening test detail	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	TP	FN	TN	FP
Jessa, 2012 Study 2 <i>From prior report</i>	CVS Optimal	Gold standard eye exam	SAIEC	High contrast VA >0.19 logMAR	0.77 (0.69-0.84)	0.73 (0.62-0.82)	2.85 (CI not calculable)	0.32 (CI not calculable)	NR	NR	NR	NR
McMurdo, 1988 <i>From prior report</i>	Physical examination	Ophthalmologic examination	Cataract	Positive finding on physical examination	1.00 (0.69-1.00)	1.00 (0.91-1.0)	Not calculable	Not calculable	10	0	40	0
McMurdo, 1988 <i>From prior report</i>	Physical examination	Ophthalmologic examination	AMD	Positive finding on physical examination by geriatrician	0.80 (0.28-0.99)	1.00 (0.92-1.0)	Not calculable	0.20 (0.03-1.15)	4	1	45	0
Swanson, 2009 <i>From prior report</i>	MDS Vision Patterns section	ETDRS chart, VA	Distance acuity	MDS Vision Patterns section score ≥ 1 , $< 20/40$	0.52 (0.45-0.59)	0.75 (0.68-0.82)	2.11 (1.56-2.86)	0.64 (0.54-0.75)	110	101	119	39
Swanson, 2009 <i>From prior report</i>	MDS Vision Patterns section	Lighthouse Near VA Chart	Near acuity	MDS Vision Patterns section score ≥ 1 , $< 20/40$	0.44 (0.39-0.50)	0.74 (0.63-0.83)	1.71 (1.16-2.53)	0.75 (0.64-0.88)	128	160	60	21
Woods, 1998 <i>From prior report</i>	VA testing, Snellen	Ophthalmologic examination	Any ocular disease, excluding refractive error	Near VA $\leq 20/30$	0.77 (0.75-0.79)	0.68 (0.65-0.71)	2.41 (2.20-2.64)	0.34 (0.31-0.38)	1113	333	732	344
Woods, 1998 <i>From prior report</i>	VA testing, Snellen	Ophthalmologic examination	Any ocular disease, excluding refractive error	Presenting distance VA $\leq 20/30$	0.74 (0.72-0.76)	0.87 (0.84-0.89)	5.69 (4.86-6.66)	0.30 (0.27-0.33)	1070	376	936	140

Abbreviations: AMD = age-related macular degeneration; CI = confidence interval; CVS = computerized vision screener; ETDRS = Early Treatment Diabetic Retinopathy Study; FN = false negative; FP = false positive; logMAR = logarithmic minimum angle of resolution; MDS = minimum data set; SAIEC = significant activity-impairing eye conditions; TN = true negative; TP = true positive; VA = visual acuity.

Appendix B Table 5. Diagnostic Accuracy of Vision Screening Tests, Quality Assessment

Author, year	Patient selection: Was a consecutive or random sample of patients enrolled?	Patient selection: Was a case-control design avoided?	Patient selection: Did the study avoid in-appropriate exclusions?	Index test(s): Were the index test results interpreted without knowledge of the results of the reference standard?	Index test(s): If a threshold was used, was it pre-specified?	Reference standard: Is the reference standard likely to correctly classify the target condition?	Reference standard: Were the reference standard results interpreted without knowledge of the results of the index test?	Flow and timing: Was there an appropriate interval between index test(s) and reference standard? (≤ 3 months)	Flow and timing: Did all (>95%) patients receive a reference standard?	Flow and timing: Did patients receive the same reference standard?	Flow and timing: Were all patients included in the analysis?	Quality rating
Ariyasu 1996 <i>From prior report</i>	Yes	Yes	Yes	Yes	No	Yes	No	Unclear	Yes	Yes	Unclear	Fair
Arora 2014 <i>New</i>	Unclear (convenience sample), Snellen used to determine eligibility	Yes	Unclear	Yes	No	Yes	Unclear	Unclear, likely	Yes	Yes	Yes	Fair
Ivers 2001 Blue Mountains Eye Study <i>From prior report</i>	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	No 82% did	Yes	No	Fair
Jessa, 2012 Study 1 and 2 <i>From prior report</i>	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Fair
McMurdo, 1988 <i>From prior report</i>	Yes	Yes	Unclear	Yes	Not applicable	Yes	Yes	Unclear, likely	Yes	Yes	Fair	Fair

Appendix B Table 5. Diagnostic Accuracy of Vision Screening Tests, Quality Assessment

Author, year	Patient selection: Was a consecutive or random sample of patients enrolled?	Patient selection: Was a case-control design avoided?	Patient selection: Did the study avoid in-appropriate exclusions?	Index test(s): Were the index test results interpreted without knowledge of the results of the reference standard?	Index test(s): If a threshold was used, was it pre-specified?	Reference standard: Is the reference standard likely to correctly classify the target condition?	Reference standard: Were the reference standard results interpreted without knowledge of the results of the index test?	Flow and timing: Was there an appropriate interval between index test(s) and reference standard? (≤ 3 months)	Flow and timing: Did all (>95%) patients receive a reference standard?	Flow and timing: Did patients receive the same reference standard?	Flow and timing: Were all patients included in the analysis?	Quality rating
Swanson, 2009 <i>From prior report</i>	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No (2 missing)	Fair
Woods 1998, Mitchell 1993 <i>From prior report</i>	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Varied, up to 3 years	No 77% confirmed, but 96% checked against records	Yes	No	Fair

Appendix B Table 6. Diagnostic Accuracy of Vision Screening Instruments, Study Characteristics

Study, year	Study design	Target vision condition	Screening test	Reference standard	Setting country	Screeener	N	Baseline population	Baseline vision parameters, proportion with visual conditions	Quality
Eekhof, 2000 <i>From prior report</i>	Cross-sectional	VA ≤0.3 (about 20/60 on Snellen) Difficulty with low vision chart at reading distance	Screening questions: Trouble recognizing face Trouble reading newspaper	Snellen chart and low vision chart	12 general practices Netherlands	GP	1,121 people	Mean age: 81 years	Snellen chart <0.3: 10.7% Difficulty recognizing a face: 23.0% Low vision chart difficulty: 13.4% Difficulty reading letters: 39.9%	Fair
Hiller, 1983 <i>From prior report</i>	Cross-sectional, NHANES data	VA ≤20/50 VA ≤20/100	Screening question: Trouble seeing, even wearing glasses or contact lenses	Snellen chart	Mobile examination centers United States	NHANES representatives	1,466 for 65-74 age subgroup (3,997 total, includes younger)	37% 65 to 74 years old All age groups: Female sex: 61% Race/ethniity: 79% white	Snellen 20/25 or worse: 69% Snellen 20/50 or worse: 14.7% Snellen 20/100 or wors: 3.0%	Fair
Mueller 2018 <i>New</i>	Prospective diagnostic study, cross-sectional	Geriatric syndromes, including a visual impairment component	Geriatric BAT: question about reading the newspaper	Comprehensive assessment by geriatrician using Snellen and visual field	4 primary care sites Switzerland	Family physicians or internists	85 patients	Age 69-74: 40% Age 75-84: 44% Age 85-94: 17% Female sex: 54% Country/region of birth: Switzerland 61%, European region 22%, outside European region 17%	Wearing glasses: 85% (4 missing) Impaired VA: 71%	Fair

Abbreviations: BAT = Brief Assessment Tool; GP = general practitioner; NHANES = National Health and Nutrition Examination Survey; VA = visual acuity.

Appendix B Table 7. Diagnostic Accuracy of Vision Screening Instruments, Quality Assessments

Author, year	Patient selection: Was a consecutive or random sample of patients enrolled?	Patient selection: Was a case-control design avoided?	Patient selection: Did the study avoid inappropriate exclusions?	Index test(s): Were the index test results interpreted without knowledge of the results of the reference standard?	Index test(s): If a threshold was used, was it pre-specified?	Reference standard: Is the reference standard likely to correctly classify the target condition?	Reference standard: Were the reference standard results interpreted without knowledge of the results of the index test?	Flow and timing: Was there an appropriate interval between index test(s) and reference standard? (≤ 3 months)	Flow and timing: Did all (>95%) patients receive a reference standard?	Flow and timing: Did patients receive the same reference standard?	Flow and timing: Were all patients included in the analysis?	Quality rating
Eekhof 2000 <i>From prior report</i>	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Hiller 1983 <i>From prior report</i>	Yes, used question to identify those who use glasses or contact lenses, and subset enrolled	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Fair
Mueller 2018 <i>New</i>	Yes	Yes	Yes	No	No	Yes	Yes	Unclear	Yes	Yes	No	Fair

Appendix B Table 8. Diagnostic Accuracy of Vision Screening Instruments, Results

Study, year	Screening question	Reference standard	Target vision condition	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	TP	FN	TN	FP
Eekhof, 2000 <i>From prior report</i>	Trouble recognizing face	Snellen chart	VA ≤0.3 (about 20/60 on Snellen)	0.40 (0.31-0.49)	0.19 (0.16-0.21)	0.49 (0.40-0.61)	3.23 (2.66-3.93)	49	73	185	814
Eekhof, 2000 <i>From prior report</i>	Trouble reading newspaper	Low vision chart	Difficulty with low vision chart at reading distance	0.17 (0.12-0.25)	0.33 (0.30-0.36)	0.26 (0.18-0.37)	2.47 (2.20-2.78)	26	123	322	643
Hiller, 1983 <i>From prior report</i>	Trouble seeing	Snellen chart	VA ≤20/50	0.34 (0.28-0.41)	0.84 (0.82-0.86)	2.15 (1.72-2.69)	0.78 (0.71-0.86)	74	142	1051	199
Hiller, 1983 <i>From prior report</i>	Trouble seeing	Snellen chart	VA ≤20/100	0.48 (0.32-0.63)	0.82 (0.80-0.84)	2.69 (1.94-3.74)	0.64 (0.48-0.84)	21	23	1170	252
Mueller, 2018 <i>New</i>	Trouble reading the newspaper	Snellen scale, visual field	Any visual impairment	0.81 (0.69-0.90)	0.46 (0.26-0.67)	1.5 (1.0-2.2)	0.4 (0.2-0.8)	All values reported in study	All values reported in study	All values reported in study	All values reported in study

Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive; VA = visual acuity.

Appendix B Table 9. Trials of VEGF Inhibitors

Study author, year Comparison	Study design	Number of centers country	Duration of followup	Interventions	Baseline population, including vision parameters	Inclusion/ exclusion criteria	N
MARINA Trial Rosenfeld et al, 2006 Sham-control	RCT	Multicenter (96 sites) United States	2 years	A. Ranibizumab 0.3 mg 1x/month (n=238) B. Ranibizumab 0.5 mg 1x/month (n=240) C. Sham injection (n=238)	A vs. B vs. C Mean age (SD) 77.4 (7.6) vs. 76.8 (7.6) vs. 77 (6.6) years Female 64.3% vs. 63.3% vs. 66.8% White 96.2% vs. 96.7% vs. 97.1% Mean VA letters (SD) 53.1 (12.9) vs. 53.7 (12.8) vs. 53.6 (14.1) VA, 20/40 or better 11.3% vs. 15% vs. 15.1% VA 20/200 or worse 14.7% vs. 12.9% vs. 13.4% Occult with no classic 63.4% vs. 62.1% vs. 63% Minimally classic 36.1% vs. 37.9% vs. 36.6% Predominantly classic 0% vs. 0.4% vs. 0%	Age ≥50 years with subfoveal CNV secondary to AMD and BCVA 20/40 to 20/320 with primary of recurrent CNV secondary to AMD with maximum lesion size 12 disk areas, presumed recent progression	716
MARINA Trial (Vision-related Function) Chang, 2007 Sham-control	See Rosenfeld et al, 2006	See Rosenfeld et al, 2006	See Rosenfeld et al, 2006	See Rosenfeld et al, 2006	Baseline NEI VFQ-25 scores, mean (SD) A. 68 (19.5) B. 68.1 (19.8) C. 71.7 (18.2)	See Rosenfeld et al, 2006	See Rosenfeld et al, 2006
MARINA Trial (Post-hoc analysis) Bressler, 2013 Sham-control	See Rosenfeld et al, 2006	See Rosenfeld et al, 2006	See Rosenfeld et al, 2006	See Rosenfeld et al, 2006	See Rosenfeld, 2006 A vs. B vs. C Currently driving "at least once in a while" at baseline (NEI VFQ-25 item 15) 68.1% vs. 68.2% vs. 69.6% Of those driving at baseline, mean VA letter score 72.6 vs. 74 vs. 75.5	See Rosenfeld et al, 2006; anyone who completed any portion of the NEI VFQ-25 at baseline	716

Appendix B Table 9. Trials of VEGF Inhibitors

Study author, year Comparison	Study design	Number of centers country	Duration of followup	Interventions	Baseline population, including vision parameters	Inclusion/ exclusion criteria	N
PIER Study (Year 1) Regillo, 2008 Sham-control	RCT	Multicenter (43 sites) United States	1 year	A. Ranibizumab 0.3 mg B. Ranibizumab 0.5 mg C. Sham injection Dosing 1x/month for 3 months followed by 1x every 3 months	Mean age ~78 years Female 54.1% to 68.3% White 91.8% to 95% Baseline mean VA 53 to 56 letters 20/40 to 20/200 59% to 81.7% Occult with no classic CNV 43% Minimally classic 38% Predominantly classic 19%	Age ≥50 years with primary or recurrent subfoveal CNV secondary to AMD, BCVA 20/40 to 20/320, total CNV area composing minimum 50% total AMD lesion area, maximum lesion size 12 disk areas, presumed disease progression (if no classic CNV), no prior PDT or antiangiogenic drug trial	184
VISION Trials (2 trials) Gragoudas, 2004 Sham-control	RCT	Multicenter (117 sites) United States, Canada, Europe, Israel, Australia, South America	48 weeks	A. Pegaptanib 0.3 mg B. Pegaptanib 1.0 C. Pegaptanib 3.0 mg, all Pegaptanib doses every 6 weeks up to 48 weeks (9 treatments) D. Sham injection	Mean age NR Age range 50-64 years: 6%; 65-74 years: 32%; 75-84 years: 52%; ≥85 years: 10% 58% female 96% white; 4% other Mean VA, study eye 51.8 letters (SD 12.8) Occult 38% Minimally classic 36% Predominantly classic 26%	Age ≥50 years with subfoveal CNV secondary to AMD, BCVA 20/40 to 20/320 in study eye and 20/800 or better in other eye, maximum lesion size 12 disk areas	Randomized: 1,208 Analyzed: 1,186
RIVAL Trial Gillies, 2019 Newer vs. older	RCT	Multicenter (24 sites) Australia	24 months	A. 2 mg aflibercept B. 0.5 mg ranibizumab Dosing 1x for 3 months, followed by treatment extension (every 4 if disease activity, or up to max every 12 if no sign of	Mean age 79 years vs. 77 years Female 55% vs. 51% Total BCVA letter score (logMAR) 65 (13) vs. 65 (15) Proportion with MA: 6% vs. 7% History smoking: 52% vs. 53% History of ATE: 17% vs. 9% Family history AMD: 19% vs. 21%	Age ≥50 with CNV secondary to AMD and VA letter score ≥23	Randomized: 298 Analyzed: 278 Attrition: 30

Appendix B Table 9. Trials of VEGF Inhibitors

Study author, year Comparison	Study design	Number of centers country	Duration of followup	Interventions	Baseline population, including vision parameters	Inclusion/ exclusion criteria	N
				disease; in followup, interval decreased by every 2 for every sign of disease activity)			
VIEW Trials (2 trials) Heier, 2012 (Year 1) Waldstein, 2016 Ho, 2018 Newer vs. older	RCT	Multicenter VIEW 1, 154 sites, United States and Canada VIEW 2, 172 sites, international	52 weeks	3 loading doses of A-D, followed by additional treatment or sham injection (up to 1 year) as needed A. IAI 2mg every 4 weeks B. IAI 0.5mg every 4 weeks C. IAI 2mg every 8 weeks D. Ranibizumab 0.5mg every 4 weeks	Mean age (SD) 73 years (9) to 78.4 years (8.1) White 70.9% to 97.4% Female 49.7% to 63.8% ETDRS BCVA mean (SD) 51.6 (13.9) to 55.7 (12.8) ≥20/40 BCVA 2.6% to 6.6% Predominantly classic 23.3% to 28.8% Minimally classic 32.2% to 36.5% Occult 35.9% to 40.2% Mean lesion size (SD) 6.89 mm ² (5.2) to 8.72 mm ² (6.1) Mean (SD) baseline NEI VFQ-25 scores (0-100, 100=best) 69.6 (16.8) to 74 (18.2)	Age ≥50 years with active subfoveal CNV lesions secondary to AMD; CNV ≥50% total lesion size; BVCA between 73 and 25 ETDRS letters (20/40 to 20/320 Snellen equivalent); no prior treatment for AMD in study eye	Randomized: 2,457 Analyzed: 2,412 Attrition: 217
Continued from above VIEW Trials (2 trials) Heier, 2012 (Year 1) Waldstein, 2016 Ho, 2018 Newer vs. older	See Heier 2012	See Heier 2012	See Heier 2012	See Heier 2012	See Heier 2012	See Heier 2012	See Heier 2012

Appendix B Table 9. Trials of VEGF Inhibitors

Study author, year Comparison	Vision-related outcomes	Other outcomes	Adverse events	Quality
MARINA Trial Rosenfeld et al, 2006 Sham-control	<p>A vs. B vs. C</p> <p>12 months</p> <p>VA gain ≥15 letters: 24.8% vs. 33.8% vs. 5.0%</p> <p>VA, loss <15 letters: 94.5% vs. 94.6% vs. 62.2%</p> <p>VA 20/40 or better: 38.7% vs. 40% vs. 10.9%</p> <p>VA, 20/200 or worse: 12.2% vs. 11.7% vs. 42.9%</p> <p>Mean VA change from baseline, letters: 6.5 vs. 7.2 vs. -10.4</p> <p>24 months</p> <p>VA, gain ≥15 letters: 26.1% vs. 33.3% vs. 3.8%</p> <p>VA, loss <15 letters: 92% vs. 90% vs. 52.9%</p> <p>VA, 20/40 or better: 34.5% vs. 42.1% vs. 5.9%</p> <p>VA, 20/200 or worse: 14.7% vs. 15% vs. 47.9%</p> <p>Mean VA change from baseline, letters: 5.4 vs. 6.6 vs. -14.9</p>	<p>A + B vs. C:</p> <p>All-cause mortality: 2.3% (11/478) vs. 2.5% (6/238); RR 0.91, 95% CI 0.34 to 2.44</p> <p>Vascular mortality: 1.3% (6/478) vs. 1.7% (4/236); RR 0.74, 95% CI 0.21 to 2.60</p> <p>A vs. B vs. C</p> <p>Death (nonvascular): 0.8% (2/238) vs. 1.3% (3/239) vs. 0.8% (2/236)</p> <p>Death (APTC): 1.3% (3/238) vs. 1.3% (3/239) vs. 1.7% (4/236)</p> <p>Vision related QoL (NEI-VFQ), mean change from baseline:</p> <p>1-year followup, composite score (95% CI): 5.2 (3.5 to 6.9) vs. 5.6 (3.9 to 7.4) vs. -2.8 (-4.6 to -1.1); ranibizumab vs. sham p<0.01</p> <p>General health score: -2.6 (-5.0 to 0.2) vs. -5.1 (-7.6 to -2.6) vs. -6.9 (-9.6 to -4.3); ranibizumab vs. sham p=NS</p> <p>Mental health score: 12.0 (9.4 to 14.6) vs. 13.1 (10.0 to 16.2) 3.3 (0.5 to 6.1); ranibizumab vs. sham p<0.01</p> <p>Social functioning score: 3.1 (0.3 to 5.9) vs. 3.8 (1.2 to 6.3) vs. -5.1 (-7.7 to -2.5); ranibizumab vs. sham p<0.01</p> <p>Driving score: -2.1 (-5.9 to 1.7) vs. -0.4 (-3.8 to 3.0) vs. -12.4 (-16.0 to -8.7); ranibizumab vs. sham p<0.0</p> <p>12-year followup, composite score: 4.8 (2.9 to 6.8) vs. 4.5 (2.5 to 6.5) vs. -6.5 (-8.4 to -4.6); ranibizumab vs. sham p<0.01</p> <p>General health score: -5.7 (-8.6 to -2.8) vs. -6.7 (-9.6 to -3.8) vs -9.0 (-12.0 to -6.2); ranibizumab vs. sham p=NS</p> <p>Mental health score: 11.9 (8.9 to 14.9) vs 12.6 (9.4 to 15.8) vs. -0.7 (-3.7 to 2.4); ranibizumab vs. sham p<0.01</p> <p>Social functioning score: 1.9 (-1.1 to 4.9) vs. 1.4 (-1.6 to 4.3) vs. -9.5 (-12.0 to -6.5); ranibizumab vs. sham p<0.01</p> <p>Driving score: -1.6 (-5.7 to 2.5) vs. -2.7 (-6.3 to 0.9) vs. -17.1 (-21.0 to -13.0); ranibizumab vs. sham p<0.01</p>	<p>A vs. B vs. C</p> <p>Endophthalmitis: 0.8% (2/38) vs. 1.3% (3/239) vs. 0/236</p> <p>Uveitis: 1.3% (3/238) vs. 1.3% (3/239)) vs. 0/238</p> <p>Retinal detachment: 0/238 vs. 0/239 vs. 0.4% (1/236)</p> <p>Vitreous hemorrhage: 0.4% (1/238) vs. 0.4% (1/239) vs. 0.8% (2/236)</p> <p>Investigator-defined HTN: 17.2% (41/238) vs. 16.3% (39/239) vs. 16.1% (38/236)</p> <p>Total serious and nonserious events, nonocular hemorrhage: 9.2% (22/238) vs. 8.8% (21/239) vs. 5.5% (13/236)</p> <p>Reported as serious event, nonocular hemorrhage: 1.3% (3/238) vs. 2.1% (5/239) vs. 0.8% (2/236)</p> <p>A + B vs. C:</p> <p>MI: 1.9% (9/478) vs. 1.7% (4/238); RR 1.12, 95% CI 0.35 to 3.60</p> <p>CVA: 1.9% (9/478) vs. 0.8% (2/238); RR 2.24, 95% CI 0.49 to 10</p> <p>A vs. B vs. C</p> <p>APTC ATE: 4.6% vs. 4.6% vs. 3.8%</p> <p>Nonfatal MI: 2.5% (6/238) vs. 1.3% (3/239) vs. 1.7% (4/236)</p> <p>Stroke: 1.3% (3/238) vs. 2.5% (6/239) vs. 0.8% (2/236)</p>	Good

Appendix B Table 9. Trials of VEGF Inhibitors

Study author, year Comparison	Vision-related outcomes	Other outcomes	Adverse events	Quality
MARINA Trial (Vision-related Function) Chang, 2007 Sham-control	<p>A vs. B vs. C</p> <p>Mean change NEI VFQ-25 scores from baseline, 12 months (95% CI): 5.2 (3.5 to 6.9) vs. 5.6 (3.9 to 7.4) vs. -2.8 (-4.6 to -1.1); A or B vs. C, p<0.001</p> <p>Mean change NEI VFQ-25 scores from baseline, 24 months (95% CI): 4.8 (2.9 to 6.8) vs. 4.5 (2.5 to 6.5) vs. -6.5 (-8.4 to -4.6); A or B vs. C, p<0.001</p> <p>Subscale changes from baseline to 12 months</p> <p>Mean change near-activities subscale score (95% CI): 9.4 (6.8 to 12) vs. 10.4 (8.1 to 12.8) vs. -2.6 (-4.9 to -0.2)</p> <p>Mean change distance-activities subscale score (95% CI): 6.7 (4.3 to 9.2) vs. 7 (4.8 to 9.2) vs. -5.9 (-8.2 to -3.6)</p> <p>Mean change dependency subscale score (95% CI): 3.6 (0.6 to 6.6) vs. 6.8 (4.1 to 9.6) vs. -4.7 (-7.8 to -1.6)</p> <p>p<0.001 for A or B vs. C, all subscales</p>	See Rosenfeld et al, 2006	See Rosenfeld et al, 2006	See Rosenfeld et al, 2006
MARINA Trial (Post-hoc analysis) Bressler, 2013 Sham-control	<p>Only B vs. C reported</p> <p>12 months</p> <p>VA 20/40 or better in 1 or both eyes (95% CI): 91% (86 to 96) vs. 83% (76 to 89)</p> <p>Of those <70 letters in both eyes at baseline, achieve a letter score of ≥70 in 1 or both eyes at followup (95% CI): 36% (27 to 44) vs. 11% (5 to 16%)</p> <p>24 months</p> <p>VA 20/40 or better in 1 or both eyes (95% CI): 85% (79 to 92) vs. 75% (68 to 83)</p> <p>Of those <70 letters in both eyes at baseline, achieve a letter score of ≥70 in 1 or both eyes at followup (95% CI): 41% (33 to 50) vs. 8% (3 to 13)</p>	<p>A vs. B vs. C; p-values for B vs. C</p> <p>12 months</p> <p>Currently driving at least once in a while: 65.5% vs. 64.3% vs. 52.1%, p=0.01</p> <p>Mean change in driving function subscale (95% CI): -2.1 vs. -0.04 vs. -12.5; treatment difference B vs. C 12.1 (7.1 to 17.1), p<0.001</p> <p>24 months</p> <p>Currently driving at least once in a while: 60.4% vs. 57.5% vs. 49.2%, p>0.05</p> <p>Mean change in driving function subscale (95% CI): -2.1 vs. -2.8 vs. -17.3; treatment difference B vs. C 14.5 (8.9 to 20.1), p<0.001</p>	<p>A vs B</p> <p>CVA: 3.3% (8/239) vs. 1.3% (3/236); RR 2.63 (95% CI 0.71 to 9.81)</p> <p>B vs. C</p> <p>CVA: 1.3% (3/238) vs. 1.3% (3/326); RR 0.99 (95% CI 0.20 to 4.86)</p>	Good

Appendix B Table 9. Trials of VEGF Inhibitors

Study author, year Comparison	Vision-related outcomes	Other outcomes	Adverse events	Quality
PIER Study (Year 1) Regillo, 2008 Sham-control	A vs. B vs. C at 1 year VA, gain ≥15 letters: 11.7% vs. 13.1% vs. 9.5% VA, loss <15 letters: 83.3% vs. 90.2% vs. 49.2%; A or B vs. C, p<0.001 VA, 20/200 or worse: 23.3% vs. 24.6% vs. 52.4%; A or B vs. C, p<0.001 Mean VA change (ETDRS) letters from baseline: -1.6 vs. -0.2 vs. -16.3; A or B vs. C, p<0.001	A vs. B vs. C Clinically meaningful (≥10-point increases) in the near activities NEI VFQ-25 subscale scores: 32% vs. 31% vs. 14%; A or B vs. C, p<0.05 Adherence: ≥85% received each scheduled injection Death: 0 vs. 0 vs. 0	A vs. B vs. C Serious ocular AE Ocular hemorrhage: 3.4% (2/59) vs. 0 (0/61) vs. 3.2% (2/63) Macular edema: 1.7% (1/59) vs. 0 vs. 3.2% (2/63) Non-ocular AE Non-ocular hemorrhage: 3.4% (2/59) vs. 6.6% (4/61) vs. 4.8% (3/63) HTN: 6.8% (4/59) vs. 9.8% (6/61) vs. 8.1% (5/63) MI: 0 vs. 0 vs. 0C VA: 0 vs. 0 vs. 0 Ischemic cardiomyopathy: 0 vs. 0 vs. 1	Good
VISION Trials (2 trials) Gragoudas, 2004 Sham-control	A vs. B vs. C vs. D Gain ≥15 letters: 6% (18/294) vs. 7% (20/300) vs. 4% (13/296) vs. 2% (6/296); A (p=0.04) and B (p=0.02) vs. D Loss <15 letters: 70% (206/294) vs. 71% (213/300) vs. 65% (193/296) vs. 55% (164/296); A and B (p<0.001) and C (p=0.03) vs. D Loss ≥30 letters: 10% (28/294) vs. 8% (24/300) vs. 14% (40/296) vs. 22% (65/296), all p=0.01 or better vs. D VA 20/200 or worse: 38% (111/293) vs. 43% (128/300) vs. 44% (129/296) vs. 56% (165/296), all p=0.001 or better vs. D	PDT administration after baseline: 17% (49/294) vs. 18% (55/300) vs. 19% (57/296) vs. 21% (62/296) Peg vs. sham Death: 2% in all groups	Peg vs. sham Discontinuation for any cause: 1% in all groups Vascular HTN: 10% in all groups Hemorrhagic events: 2% vs. 3% Thromboembolic events: 6% in all groups Eye pain: 34% vs. 28% Vitreous floaters: 33% vs. 8%, p<0.001 Punctate keratitis: 32% vs. 27% Cataracts: 20% vs. 18% Vitreous opacities: 18% vs. 10%, p<0.001 Anterior-chamber inflammation: 14% vs. 6%, p=0.001 Visual disturbance: 13% vs. 11% Specific injection-related AE in first 12 months Endophthalmitis 1.3% (12/890) Traumatic injury to the lens: 0.6% (5/890) Retinal detachment: 0.7% (6/890) From D'Amico 2006, year 1: Peg (n=892) vs. sham (298) All serious thromboembolic events: 4% vs. 4% Serious hemorrhagic AEs: 1% vs. 1%	Good

Appendix B Table 9. Trials of VEGF Inhibitors

Study author, year Comparison	Vision-related outcomes	Other outcomes	Adverse events	Quality
<p>RIVAL TrialGillies, 2019 Newer vs. older</p>	<p>A vs. B at month 24 Mean change (SD) in BCVA letter score: 5.3 (13.3) vs. 6.5 (14.4) Gained ≥15 letters: 19% (20/108) vs. 25% (29/117); OR 1.61 (0.77 to 3.35); p=0.21 Lost <15 letters: 94% (102/108) vs. 94% (110/117); OR 0.94 (0.30 to 2.90); p=0.91 Change in BCVA from baseline, LSM (95% CI): 4.6 (2.7 to 6.6) vs. 6.6 (4.7 to 8.5); difference 2.0 (-0.7 to 4.6), p=0.15 Mean change square root area of MA, mm (95% CI): +28 (0.19 to 0.37) vs. +0.36 (0.27 to 0.45); difference +0.08 (-0.05 to 0.21); p=0.24 Proportion of patients with MA: 32% (35/108) vs. 37% (43/117); OR 1.19 (0.67 to 2.09); p=0.55</p>	<p>Mean number injections (SD): 17 (6.3) vs. 17.7 (6.4)</p>	<p>A vs. B Any AE: 93.5% (130/139) vs. 88.7% (125/141) Ocular AEs: 82.7% (115/139) vs. 71.6% (101/141) Retinal hemorrhage: 5.0% (7/139) vs. 5.0% (7/141) CNV: 5.8% (8/139) vs. 5.7% (8/141) Eye pain: 17.3% (24/139) vs. 17% (24/141) Ocular serious AEs: 2.9% (4/139) vs. 1.4% (2/141) Retinal detachment: 1.4% (2/139) vs. 0 Endophthalmitis: 1.4% (2/139) vs. 0 Any ATE: 5% (7/139) vs. 7.8% (11/141) APTC ATE: 3.6% (5/139) vs. 5.7% (8/141) Non-fatal MI: 0.7% (1/139) vs. 1.4% (2/141) Non-fatal stroke: 2.9% (4/139) vs. 4.3% (6/141) Discontinuation due to AE: 10% (14/139) vs. 6% (9/141) Discontinuation due to serious AE: 10% (14/139) vs. 5% (7/141) Death: 4.3% (6/139) vs. 2.1% (3/141)</p>	<p>Good</p>
<p>VIEW Trials (2 trials) Heier, 2012 (Year 1) Waldstein, 2016 Ho, 2018 Newer vs. older</p>	<p>A vs. B vs. C vs. D *Objective is statistical noninferiority Losing <15 ETDRS letters, IAI vs. D: 94.9% [1725/1817] vs. 94.3% [561/595] Gaining ≥15 ETDRS letters, IAI vs. D: 31.4% [571/1817] vs. 32.4% [193/595] VIEW1 Proportion losing <15 ETDRS letters: 95.1% [289/304] vs. 95% [286/301] vs. 94.4% [284/301] vs. 93.8% [285/304] Mean change in ETDRS BCVA (SD): 10.9 (13.8) vs. 6.9 (13.4) vs. 7.9 (15) vs. 8.1 (15.3); A vs. D, p=0.005 Proportion gaining ≥15 ETDRS letters: 37.5% [114/304] vs. 24.9% [75/301] vs. 30.6% [92/301] vs. 30.9% [94/304]</p>	<p>Mean number active injections (out of 13 possible, for every 4 injections): 12.1 to 12.5 for both VIEW studies Mean number active injections (out of 8, for every 8 injections): 7.5 for both VIEW studies Resolution of intraretinal cystoid fluid, baseline to 52 weeks, C vs. D: 50.1% vs. 52.4%; adjusted difference -2.3 (-9.28 to 4.74) Resolution of subretinal fluid, baseline to 52 weeks, C vs. D: 75% vs. 66.2%; adjusted difference 8.7 (2.35 to 15.15) Resolution of pigment epithelial detachment, baseline to 52 weeks, C vs. D: 34.1% vs. 28.1%; adjusted difference 6.0 (-0.37 to 12.32) Presence of retinal morphology at baseline impact on BCVA at 52 weeks</p>	<p>A vs. B vs. C vs. D Rate of events per 1,000 injections (eye disorders, endophthalmitis, procedural complications, increased IOP): 0.8 vs. 0.1 vs. 0.2 vs. 1.1 ≥1 Ocular TEAE VIEW1: 75% [228/304] vs. 74.3% [226/304] vs. 78.5% [238/303] vs. 80.9% [246/304] VIEW2: 61.8% [191/309] vs. 61.3% [182/297] vs. 64.5% [198/307] vs. 64.3% [187/291] Ocular TEAE >10% in population VIEW1 conjunctival hemorrhage: 35.9% [109/304] vs. 39.5% [120/304] vs. 43.2% [131/303] vs. 47.4% [144/304]</p>	<p>Good</p>

Appendix B Table 9. Trials of VEGF Inhibitors

Study author, year Comparison	Vision-related outcomes	Other outcomes	Adverse events	Quality
	<p>Mean change in total NEI VFQ-25 score (SD): 6.7 (13.5) vs. 4.5 (11.9) vs. 5.1 (14.7) vs. 4.9 (14)</p> <p>VIEW2</p> <p>Proportion losing <15 ETDRS letters: 94.5% [292/309] vs. 95.3% [282/296] vs. 95.4% [292/306] vs. 94.8% [276/291]</p> <p>Mean change in ETDRS BCVA (SD): 7.6 (12.6) vs. 9.7 (14.1) vs. 8.9 (14.4) vs. 9.4 (13.5)</p> <p>Proportion gaining ≥15 ETDRS letters: 29.4% [91/309] vs. 34.8% [103/296] vs. 31.4% [96/306] vs. 30.9% [94/304]</p> <p>Mean change in total NEI VFQ-25 score (SD): 4.5 (15) vs. 5.1 (13.7) vs. 4.9 (14.7) vs. 6.3 (14.8)</p>	<p>Intraretinal cystoid: -2.77 letters (p<0.001)</p> <p>Subretinal fluid: 2.11 letters (p=0.02)</p> <p>Pigment epithelial detachment: -1.88 letters (p=0.01)</p> <p>Vascular death: 0.5% (9/1824) vs. 0.3% (2/595)</p> <p>Vascular death: VIEW1 0 vs. 0.3% vs. 1.3% vs. 0.3%; VIEW2 0.3% vs. 0.7% vs. 0.3% vs. 0.3%</p> <p>Effects of aflibercept and ranibizumab were also similar when patients were stratified according to age, baseline visual acuity, baseline lesion size or type of choroidal neovascularization, and baseline central retinal thickness</p>	<p>VIEW2 VA reduced: 8.4% [26/309] vs. 11.4% [34/297] vs. 10.7% [33/307] vs. 6.9% [20/291]</p> <p>VIEW2 conjunctival hemorrhage: 7.8% [24/309] vs. 12.5% [37/297] vs. 9.8% [30/307] vs. 7.9% [23/291]</p> <p>≥1 Non-Ocular TEAE</p> <p>VIEW1: 72.4% [220/304] vs. 76% [231/304] vs. 73.6% [223/303] vs. 77% [234/304]</p> <p>*Infections and gastrointestinal disorders were most common, but no individual AEs were >10%</p> <p>VIEW2: 74.8% [231/309] vs. 69.4% [206/297] vs. 69.4% [213/307] vs. 62.2% [181/291]</p> <p>*Infections, investigations (blood glucose and ECG T wave inversion), and cardiac and gastrointestinal disorders were most common, but no individual AEs were >10%</p>	
<p>Continued from above</p> <p>VIEW Trials (2 trials)</p> <p>Heier, 2012 (Year 1)</p> <p>Waldstein, 2016</p> <p>Ho, 2018</p> <p>Newer vs. older</p>	<p>Mean change in ETDRS BCVA at 52 weeks by baseline age (range)</p> <p><65 years: 11.5 to 14.8 letters</p> <p>65-75 years: 8.4 to 10.1 letters</p> <p>>75 years: 7.2 to 8.1 letters</p> <p>Mean change in ETDRS BCVA at 52 weeks by baseline BCVA (range)</p> <p><35 letters: 13.2 to 17.2 letters</p> <p>35-50 letters: 9.7 to 13.3 letters</p> <p>>50 letters: 6.5 to 8.0 letters</p> <p>Mean change in ETDRS BCVA at 52 weeks by baseline lesion type (range)</p> <p>Occult: 6.7 to 8.8 letters</p> <p>Minimally classic: 7.3 to 9.8 letters</p> <p>Predominantly classic: 9.3 to 11.9 letters</p>	<p>See Heier 2012</p>	<p>MI: 0.8% (14/1824) vs. 1% (6/595)</p> <p>CVA: 0.4% (7/1824) vs. 0.2% (1/595)</p> <p>APTC Arteriothrombotic Event: View1 0.7% vs. 2.3% vs. 2.0% vs. 1.6%; VIEW2 1.3% vs. 1.7% vs. 2.6% vs. 1.7%</p> <p>Nonfatal MI: VIEW1 0.3% vs. 1.3% vs. 0.3% vs. 1.3%; VIEW2 0.6% vs. 0.7% vs. 1.6% vs. 0.7%</p> <p>Nonfatal stroke: VIEW1 0.3% vs. 0.7% vs. 0.3% vs. 0%; VIEW2 0.3% vs. 0.3% vs. 0.7% vs. 0.7%</p> <p>Any AE of HTN: VIEW1 8.2% vs. 8.6% vs. 10.2% vs. 9.5%; VIEW2 10.0% vs. 7.4% vs. 9.1% vs. 10.0%</p> <p>Venous thromboembolic event: VIEW1 0 vs. 0.3% vs. 0 vs. 0.3%; VIEW2 0 vs. 0 vs. 0 vs. 0</p> <p>Congestive heart failure event: VIEW1 0.3% vs. 0.7% vs. 1.0% vs. 0.7%; VIEW2 0 vs. 0 vs. 0.3% vs. 0.3%</p>	<p>See Heier 2012</p>

Appendix B Table 9. Trials of VEGF Inhibitors

Abbreviations: AE = adverse events; AMD = age-related macular degeneration; APTC = Antiplatelet Trialists' Collaboration; ATE = arterial thromboembolic event; BCVA = best-corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularization; CVA = cerebrovascular accident; ETDRS = Early Treatment Diabetic Retinopathy Study; HTN = hypertension; IAI = intravitreal aflibercept injection; IOP = intraocular pressure; logMAR = logarithmic minimum angle of resolution; LSM = least-squared mean; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; MI = myocardial infarction; nAMD = non-age-related macular degeneration; NEI VFQ = National Eye Institute Visual Function Questionnaire; NR = not reported; NS = not significant; PDT = photodynamic therapy; PIER = PIER study; QoL = quality of life; RCT = randomized controlled trial; RIVAL = A Randomized Clinical Trial Comparing Ranibizumab and Aflibercept; RR = relative risk; SD = standard deviation; TEAE = treatment emergent adverse events; VA = visual acuity; VIEW = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD; VISION = VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group study.

Appendix B Table 10. Trials of VEGF Inhibitors, Quality Assessment

Comparison	Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential/high?	People analyzed in the groups in which they were randomized?	Quality
Sham-control	MARINA Rosenfeld 2006	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
	PIER Regillo 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes (1-year results only)	Good
	VISION Gragoudas 2004	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Newer vs. older	RIVAL Trial Gillies 2019	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Good
	VIEW1 and 2 Heier 2012	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Good

Abbreviations: MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PIER = PIER study; RIVAL = A Randomized Clinical Trial Comparing Ranibizumab and Aflibercept; VIEW = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD; VISION = VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group study.

Appendix B Table 11. AREDS Trials of Multivitamins

Author, year study name	Study design	Country setting	Inclusion criteria	Randomized analyzed attrition	Intervention
AREDS Research Group, 2001 AREDS Report No. 8 Johnson 2007 Original publication	Placebo-controlled trial	United States 11 centers	Age 55 to 80 years with extensive small drusen, intermediate drusen, large drusen, noncentral geographic atrophy, or pigment abnormalities in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye; at least 1 eye had BCVA of 20/32 or better	Randomized: 4,757 Enrolled in AMD trial after categorization: 3,640 Analyzed: 3,609 Attrition: 2.4%	A. Antioxidant supplement: 500 mg vitamin C + 400 IU vitamin E + 15 mg beta carotene/day (n=945) B. Zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide (n=904) C. Antioxidant supplement + zinc (n=888) D. Placebo (n=903)
Chew, 2013 AREDS Report No. 35 10-year followup	RCT (long-term observational followup)	United States 11 centers	Age 55 to 80 years with AMD and BCVA \geq 20/32 in at least one eye	Enrolled: 3,549 (of original 4,757 trial population)Analyzed:3,476 (AREDS categories 2, 3, and 4 AMD)Attrition: 4%	A. Antioxidant supplement (vitamin C 500 mg + vitamin E 400 IU + beta-carotene, 15 mg/day) (n=891) B. Zinc 80 mg/day (n=865) C. Antioxidant supplement + zinc (n=859) D. Placebo (n=861)
AREDS 2004 Report No. 12 Cognition	RCT (observational followup)	See above	See above	2,166 of the larger sample completed the cognitive battery	A. Antioxidant supplement (vitamin C 500 mg + vitamin E 400 IU + beta-carotene, 15 mg/day) (n=566) B. Zinc 80 mg/day (n=538) C. Antioxidant supplement + zinc (n=528) D. Placebo (n=534)
Chew, 2009 AREDS Report No. 25 Cataract surgery	RCT (long-term observational followup)	United States Multi-center	Age 55 to 80 years with AMD and BCVA \geq 20/32 in at least one eye	Randomized: 4,757 Analyzed (post-trial followup): 4,577 Attrition: NA	A. Any AREDS active treatment B. Placebo
AREDS2 JAMA 2013 309;(19): 2005-2015. Chew 2012, Report #1 Original publication Chew 2015, cognition	RCT	United States 82 clinical centers	Age 50 to 85 years with readable images and either bilateral large drusen or large drusen in one eye and advanced AMD (neovascular AMD or central geographic atrophy) in the fellow eye (AREDS Simple Scale Score of 2, 3, or 4) Exclude: Those with other ocular diseases or diseases that might confound the assessment of the ocular outcome measurements; cataract surgery \leq 3 months	Randomized: 4,203 (6,916 eyes) Analyzed: 4,176 (6,891 eyes) Attrition: 1% Secondary randomization regarding AREDS formula substitutions: Randomized: 3,036 (1,167 refused secondary randomization) Analyzed: 3,017 Attrition: 1%	<u>Primary randomization:</u> A. Lutein 10mg + zeaxanthin 2mg + omega-3 long-chain polyunsaturated fatty acid supplementation (EPA 650mg + DHA 350mg) (n=1,079; 1,754 eyes) B. Omega-3 long-chain polyunsaturated fatty acid supplementation (EPA + DHA 650mg / 350 mg) (n=1,068; 1,753 eyes) C. Lutein + zeaxanthin 10mg / 2mg (n=1,044; 1,714 eyes) D. Placebo* (n=1,012; 1,695 eyes) *Those in the placebo group were also given the AREDS supplement either within or outside of the secondary randomization for the 4 variations of the AREDS supplements; thus there is no true placebo group

Appendix B Table 11. AREDS Trials of Multivitamins

Author, year study name	Study design	Country setting	Inclusion criteria	Randomized analyzed attrition	Intervention
			prior; other intraocular surgeries; systemic diseases; poor 5-year survival		<p><u>Secondary randomization</u>: Those who consented to a second randomization were randomly assigned to:</p> <p>E. Standard AREDS (n=659; 1,101 eyes)</p> <p>F. AREDS with no beta-carotene (n=863; 1,410 eyes)</p> <p>G. AREDS with low dose zinc (n=689, 1,127 eyes)</p> <p>H. AREDS with no beta-carotene + low dose zinc (n=825; 1,349 eyes)</p> <p><u>Other</u></p> <p>Refused secondary randomization (n=1,167; 1,929 eyes) of which:</p> <p>I. 1,148 (1,897 eyes) took original AREDS</p> <p>J. 19 (32 eyes) did not take AREDS supplement</p> <p>Note: smokers were not randomized to receive beta carotene; analyses of neoplasm and lung cancer include all participants regardless of smoking status</p>

Appendix B Table 11. AREDS Trials of Multivitamins

Author, year study name	Baseline population/ study participants, including vision parameters	Duration of followup	Vision-related outcomes
<p>AREDS Research Group, 2001 AREDS Report No. 8</p> <p>Johnson 2007</p> <p>Original publication</p>	<p>Median age: 69 years Female: 56% female Race/ethnicity: 96% white, 3% black, 1% other Taking Centrum: 67% AMD Category: 2 29%, 3 44%, 4 26% Mean BCVA at baseline better than 20/32 for all participants</p>	<p>6.3 years, average</p>	<p>AMD Categories 2, 3, and 4 Progression to advanced AMD, adjusted: A vs. D: OR 0.77 (99% CI 0.56 to 1.05) B vs. D: OR 0.71 (99% CI 0.51 to 0.98) C vs. D: OR 0.68 (99% CI 0.49 to 0.93)</p> <p>Loss of ≥15 letters of VA, adjusted: A vs. D: OR 0.87 (99% CI 0.67 to 1.15) B vs. D: OR 0.82 (99% CI 0.63 to 1.08) C vs. D: OR 0.77 (99% CI 0.58 to 1.03)</p> <p>AMD Categories 3 and 4 Progression to advanced AMD, adjusted: A vs. D: OR 0.76 (99% CI 0.54 to 1.05) B vs. D: OR 0.70 (99% CI 0.50 to 0.97) C vs. D: OR 0.66 (99% CI 0.47 to 0.93)</p> <p>Loss of ≥15 letters of VA, adjusted: A vs. D: OR 0.87 (99% CI 0.65 to 1.17) B vs. D: OR 0.82 (99% CI 0.61 to 1.09) C vs. D: OR 0.75 (99% CI 0.55 to 1.02)</p> <p>ORs adjusted for age, sex, race, baseline AMD category and smoking status</p>
<p>Chew, 2013 AREDS Report No. 35 10-year followup</p>	<p>Age: <65 years: 19% 65-69 years: 32% ≥70 years: 49% % female: 57% Race/ethnicity: 97% white AMD category: 2: 29% 3: 44% 4: 26%</p>	<p>10 years</p>	<p>Participants with AMD category 2, 3 or 4 at baseline A vs. D, Loss of VA ≥15 letters ETDRS: OR 0.88 (99% CI 0.73 to 1.06) VA <20/100: OR 0.87 (99% CI 0.68 to 1.11) Progression to advanced AMD: OR 0.74 (99% CI 0.59 to 0.92) B vs. D, Loss of VA ≥15 letters ETDRS: OR 0.89 (99% CI 0.74 to 1.08) VA <20/100: OR 0.91 (99% CI 0.71 to 1.15) Progression to advanced AMD: OR 0.87 (99% CI 0.70 to 1.07) C vs. D, Loss of VA ≥15 letters ETDRS: OR 0.76 (99% CI 0.63 to 0.93) VA <20/100: OR 0.75 (99% CI 0.58 to 0.97) Progression to advanced AMD: C vs D: OR 0.69 (99% CI 0.56 to 0.86)</p>

Appendix B Table 11. AREDS Trials of Multivitamins

Author, year study name	Baseline population/ study participants, including vision parameters	Duration of followup	Vision-related outcomes
			<p>Participants with AMD category 3 or 4 at baseline A vs. D, Loss of VA \geq15 letters ETDRS: OR 0.83 (99% CI 0.67 to 1.02) VA <20/100: OR 0.82 (99% CI 0.64 to 1.07) Progression to advanced AMD: OR 0.70 (99% CI 0.56 to 0.88) B vs. D, Loss of VA \geq15 letters ETDRS: OR 0.86 (99% CI 0.70 to 1.07) VA <20/100: OR 0.88 (99% CI 0.69 to 1.14) Progression to advanced AMD: OR 0.82 (99% CI 0.66 to 1.02) C vs. D, Loss of VA \geq15 letters ETDRS: OR 0.71 (99% CI 0.57 to 0.88) VA <20/100: OR 0.72 (99% CI 0.56 to 0.94) Progression to advanced AMD: OR 0.66 (99% CI 0.53 to 0.83) Participants with AMD category 4 at baseline A vs. D, Loss of VA \geq15 letters ETDRS: OR 0.75 (99% CI 0.53 to 1.06) VA <20/100: OR 0.76 (99% CI 0.52 to 1.12) Progression to advanced AMD: OR 0.64 (99% CI 0.46 to 0.91) B vs. D, Loss of VA \geq15 letters ETDRS: OR 0.68 (99% CI 0.48 to 0.96) VA <20/100: OR 0.66 (99% CI 0.45 to 0.98) Progression to advanced AMD: OR 0.68 (99% CI 0.49 to 0.96) C vs. D, Loss of VA \geq15 letters ETDRS: OR 0.54 (99% CI 0.38 to 0.78) VA <20/100: OR 0.58 (99% CI 0.38 to 0.86) Progression to advanced AMD: C vs D: OR 0.56 (99% CI 0.40 to 0.79)</p>
AREDS 2004 Report No. 12 Cognition	Mean age: 75 years Otherwise NR	6.9 years	NR
Chew, 2009 AREDS Report No. 25 Cataract surgery	NR by treatment group for this analysis (see Chew 2013 for characteristics for the entire AREDS cohort)	Up to 11 years (mean followup NR)	NR

Appendix B Table 11. AREDS Trials of Multivitamins

Author, year study name	Baseline population/ study participants, including vision parameters	Duration of followup	Vision-related outcomes
<p>AREDS2 JAMA 2013 309;(19):2005-2015. Chew 2012, Report #1 Original publication Chew 2015, cognition</p>	<p>Median age: 74 years % female: 57% Race/ethnicity: 97% white, 2.0% Hispanic origin, 1.3% black, 1.2% Asian Pacific Islander and other, 0.8% Asian, 0.1% American Indian Current smokers: 7% Former smokers: 49% Diabetic: 13% Prior CVD: 19% Centrum Silver: 89% Statins: 44% NSAID: 11% Acetaminophen: 9% Aspirin use: 49% Bilateral, large drusen: 59% Advanced AMD in 1 eye: 32% AREDS Simple Scale Scores: 0: 0.2% 1: 1.5% 2: 15% 3: 26.5% 4: 58% Mean VA, study eyes (N=7,088): 20/20 or better: 37% <20/20 to 20/40: 51% <20/40 to 20/80: 8.6% <20/80 to 20/160: 1.5% 20/200 or worse: 2.3%</p>	<p>5 years, median</p>	<p><u>Primary randomization:</u> Progression to advanced AMD, year 5: Total experiencing at least 1 event: 1,608 people, 1,940 events, 6,891 eyes A vs. B vs. C vs. D: 30% (472 eyes, 387 people) vs. 31% (507 eyes, 416 people) vs. 29% (468 eyes, 399 people) vs. 31% (493 eyes, 406 people) A vs D: 1742 eyes, 472 events vs. 1691 eyes, 493 events, HR 0.89 (98.7% CI 0.75 to 1.06) B vs. D: 1749 eyes, 507 events vs. 1691 eyes, 493 events, HR 0.97 (98.7% CI 0.82 to 1.16) C vs. D: 1709 eyes, 468 events vs. 1691 eyes, 493 events, HR 0.90 (98.7% CI 0.76 to 1.07) Lutein + zeaxanthin vs no lutein + zeaxanthin: 3,451 eyes, 940 events vs. 3,440 eyes, 1,000 events, HR 0.91 (95% CI 0.82 to 1.00) DHA + EPA vs. no DHA + EPA: 3,491 eyes, 979 events vs. 3,400 eyes, 961 events, HR 0.98 (95% CI 0.89 to 1.08) Development of moderate or worse vision loss (reduction of ≥15 letters [3 lines] from baseline or treatment for neovascular AMD), year 5: A vs. D: HR 0.94 (95% CI 0.83 to 1.07) B vs. D: HR 0.96 (95% CI 0.84 to 1.09) C vs. D: HR 0.95 (95% CI 0.84 to 1.08) <u>Secondary randomization:</u> Progression to advanced AMD, year 5: Low zinc dose vs. control: 2,468 eyes, 726 events vs. 2,501 eyes, 704 events, HR 1.06 (95% CI 0.95 to 1.19) No beta carotene vs. control: 2,221 eyes, 647 events vs. 2,212 eyes, 622 events, HR 1.07 (95% CI 0.94-1.20)</p>

Appendix B Table 11. AREDS Trials of Multivitamins

Author, year study name	Other outcomes	Adverse events	Sponsor	Quality
<p>AREDS Research Group, 2001 AREDS Report No. 8</p> <p>Johnson 2007</p> <p>Original publication</p>	<p>Mortality A vs D: RR 1.12 (99% CI 0.80 to 1.57) B vs. D: RR 0.81 (99% CI 0.56 to 1.17) C vs. D: RR 0.87 (99% CI 0.60 to 1.25)</p> <p>Antioxidants vs. no antioxidants: RR 1.10 (99% CI 0.85 to 1.42)</p> <p>Zinc vs. no zinc: RR 0.79 (99% CI 0.61 to 1.02)</p>	<p>Of nearly 100 analyses, only causes and conditions significantly different by treatment are presented (other details NR): Yellow skin, antioxidant vs. no antioxidant arms: 8.3% vs. 6.0%, p=0.008</p> <p>Skin and subcutaneous tissue conditions, antioxidant vs. no antioxidant arms: 2.2% vs. 1.0%, p=0.03</p> <p>Self-reported anemia, zinc vs. no zinc arms: 13.2% vs. 10.2%, p=0.04</p> <p>Hospitalizations due to infections, antioxidant vs. no antioxidant arms: 1.6% vs. 0.8%, p=0.04</p> <p>Hospitalizations due to genitourinary causes, zinc vs. no zinc arms: 7.5% vs. 4.9%, p=0.001</p> <p>Hospitalizations for mild/moderate symptoms, zinc vs. no zinc arms: 9.7% vs. 7.8%, p=0.04</p> <p>Hospitalizations for mild/moderate symptoms, antioxidant vs. no antioxidant arms: 7.4% vs. 10.1%, p=0.005</p> <p>Circulatory AEs, antioxidant vs. no antioxidant arms: 0.3% vs. 0.8%, p=0.04</p> <p>Circulatory AEs, zinc vs. no zinc arms: 0.9% vs. 0.3%, p=0.01</p> <p>Chest pains, antioxidant vs. no antioxidant arms: 20.2% vs. 23.1%, p=0.03</p> <p>Sex/gender: Hospitalizations due to genitourinary causes, zinc vs. no zinc: Males: 8.6% vs. 4.4%, p<0.01 Females: 6.7% vs. 5.3%</p>	<p>National Eye Institute, National Institutes of Health, Bausch and Lomb Inc</p>	<p>Good</p>
<p>Chew, 2013 AREDS Report No. 35 10-year followup</p>	<p>Participants with AMD category 2, 3 or 4 at baseline</p> <p>A + C (antioxidant) vs. B + D (no antioxidant) All-cause mortality: 24.0% (439/1831) vs. 23.6% (427/1806); aHR* 1.06 (95% CI 0.93 to 1.21) CV mortality: aRR 1.20 (95% CI 0.97 to 1.49) Cancer mortality: aRR 1.07 (95% CI 0.83 to 1.38) Non-CV, non-cancer mortality: aRR 0.94 (95% CI 0.74 to 1.20) B + C (zinc) vs. A + D (no zinc) All-cause mortality: 22.4% (401/1790) vs. 25.2% (465/1847); aHR 0.83 (95% CI 0.73 to 0.95) CV mortality: aRR 0.80 (95% CI 0.64 to 0.99)</p>	<p>"No statistically significant increase in hospitalizations was associated with assignemnt to any of the AREDS supplements in the clinical trial during the 10-year followup in logistic regression analysis adjusted for age, sex, smoking status, and treatment." Details NR</p>	<p>National Eye Institute/ National Institutes of Health</p>	<p>Good</p>

Appendix B Table 11. AREDS Trials of Multivitamins

Author, year study name	Other outcomes	Adverse events	Sponsor	Quality
	Cancer mortality: aRR 0.84 (95% CI 0.65 to 1.08) Non-CV, non-cancer mortality: aRR 0.93 (95% CI 0.73 to 1.18) Note: HRs for mortality outcomes adjusted for age, sex, race, education, smoking status, BMI, diabetes, angina, cancer, HTN			
AREDS 2004 Report No. 12 Cognition	Cognition, A vs. B vs. C vs. D, mean scores: Logical Memory Part I, Immediate Recall: 36.3 vs. 37.1 vs. 35.5 vs. 35.6, p=0.06 Logical Memory Part II, Delayed Recall: 20.9 vs. 21.3 vs. 20.6 vs. 20.6, p=0.46 Modified MMSE: 92.7 vs. 92.7 vs. 92.5 vs. 92.1, p=0.40 Letter Fluency: 39.5 vs. 38.7 vs. 37.9 vs. 37.6, p= 0.09 Animal Category: 17.3 vs. 17.2 vs. 16.8 vs. 16.9, p=0.23 Buschke Test, Immediate Recall: 26.1 vs. 26.1 vs. 26.9 vs. 25.7, p=0.50 Buschke Test, Word List Mean: 5.8 vs. 5.8 vs. 5.8 vs. 5.7, p=0.88 Digits Backwards: 6.3 vs. 6.2 vs. 6.2 vs. 6.3, p=0.78	NR	See above	See above
Chew, 2009 AREDS Report No. 25 Cataract surgery	A vs. B Incident cataract surgery: 25.4% (798/3137) vs 25.6% (369/1440), RR 0.99 (95% CI 0.89 to 1.10)	NR	National Eye Institute/ National Institutes of Health	Good

Appendix B Table 11. AREDS Trials of Multivitamins

Author, year study name	Other outcomes	Adverse events	Sponsor	Quality
<p>AREDS2 JAMA 2013 309;(19):2005-2015. Chew 2012, Report #1 Original publication Chew 2015, cognition</p>	<p>Mortality A vs. D: HR 1.23 (95% CI 0.92-1.65) B vs. D: HR 1.13 (95% CI, 0.84-1.52) C vs. D: HR 1.04 (95% CI 0.77-1.40) Lutein + zeaxanthin main effect: HR 1.06 (95% CI 0.87-1.31) DHA + EPA main effect: HR 1.16 (95% CI 0.94-1.42) Low zinc main effect: HR 1.02 (95% CI 0.81-1.29) Beta carotene main effect: HR 1.01 (95% CI 0.78-1.31) Cognition (Chew 2015) N=3,501 underwent cognitive testing Yearly change in the composite cognitive function score: Long-chain polyunsaturated fatty acids vs. no long-chain polyunsaturated fatty acids: -0.19 (99% CI, -0.25 to -0.13) vs. -0.18 (99% CI, -0.24 to -0.12); difference in yearly change, -0.03 [99% CI, -0.20 to 0.13]; p=0.63 Lutein/zeaxanthin vs. no lutein/zeaxanthin: -0.18 (99% CI, -0.24 to -0.11) vs. -0.19 (99% CI, -0.25 to -0.13); difference in yearly change, 0.03 [99% CI, -0.14 to 0.19]; p = 0.66</p>	<p><u>Primary randomization:</u> No statistically significant in reported SAEs across groups A vs. B vs. C vs. D Participants with ≥1 SAE: 48.1% vs. 47.3% vs. 46.4% vs. 47.3% Cardiac disorders: 9.5% vs. 11.1% vs. 10.5% vs. 9.5% GI tract disorders: 5.7% vs. 5.4% vs. 6.6% vs. 7.5% Infections: 9.2% vs. 9.6% vs. 9.8% vs. 8.9% Neoplasms benign, malignant, and unspecified: 8.5% vs. 7.8% vs. 8.4% vs. 7.9% Nervous system disorders: 6.8% vs. 6.7% vs. 7.1% vs. 6.5% Respiratory tract, thoracic, and mediastinal disorders: 4.3% vs. 3.5% vs. 4.1% vs. 4.3% Incident lung neoplasm: 1.6% vs. 2.1% vs. 1.5% vs. 0.9% <u>Secondary randomization/other:</u> Excluding smokers, more lung cancers in beta carotene group than no beta carotene group: 2.0% (23) vs. 0.9% (11), p=0.04 E vs. F vs. G vs. H vs. I vs. J - No statistically significant in reported SAEs across groups Participants with >1 SAE: 50.1% vs. 47.5% vs. 50.1% vs. 47.5% vs. 43.6% vs. 52.6% Cardiac disorders: 10.5% vs. 10.4% vs. 9.6% vs. 13% vs. 8.1% vs. 15.8% GI tract disorders: 5.9% vs. 6.4% vs. 5.4% vs. 6.9% vs. 6.5% vs. 5.3% Infections and infestations: 8.5% vs. 9% vs. 9.4% vs. 10.2% vs. 9.6% vs. 5.3% Neoplasms benign, malignant, and unspecified: 9.7% vs. 7.5% vs. 9% vs. 8.1% vs. 7.2% vs. 10.5% Nervous system disorders: 7.3% vs. 6.7% vs. 8% vs. 6.5% vs. 5.7% vs. 26.3% Respiratory tract, thoracic, and mediastinal disorders: 3.2% vs. 4.6% vs. 4.4% vs. 5.2% vs. 3% vs. 5.3% Incident lung neoplasm: 1.4% vs. 1.5% vs. 2% vs. 1.6% vs. 1.2% vs. 5.3%</p>	<p>National Eye Institute/ National Institutes of Health</p>	<p>Good</p>

Abbreviations: AEs = adverse events; aHR = adjusted hazard ratio; AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Studies; aRR = adjusted relative risk; BCVA = best-corrected visual acuity; BMI = body mass index; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; ETDRS = Early Treatment Diabetic Retinopathy Study; HR = hazard ratio; HTN = hypertension; MMSE = Mini-Mental State Examination; NA = not applicable; NR = not reported; NSAID = nonsteroidal anti-inflammatory drugs; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; VA = visual acuity.

Appendix B Table 12. AREDS Trials of Multivitamins, Quality Assessment

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential or high?	People analyzed in the groups in which they were randomized?	Quality
AREDS, 2001 Report No. 8	Randomized but method not described	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Good
AREDS2, 2013 Chew 2012 Report No. 1 and AREDS2 2013, JAMA 2013;307(19): 2005-15	Yes	Likely (coordinating center)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good

Abbreviation: AREDS = Age-Related Eye Disease Studies.

Appendix B Table 13. Systematic Review of Multivitamins

Author, year	Literature databases/ date of last search	Trials/ study Ns/ countries	Baseline population, including vision parameters	Total N	Interventions
Evans 2017	<p>Cochrane Central Register of Controlled Trials, MEDLINE Ovid, Embase Ovid, AMED, OpenGrey, ISRCTN registry, United States NIH Ongoing Trials Register clinicaltrials.gov, WHO International Clinical Trials Registry Platform</p> <p>Database inception to March 2017</p>	<p>19 RCTs: AMDSG 1996: n=71, United States AREDS 2001: n=3,640, United States AREDS2 2013: n =4,203 (6,916 eyes), United States Bartlett 2007: n=30, United Kingdom Berrow 2013: n=14, United Kingdom CARMA 2013: n=433 (614 eyes), Ireland CARMIS 2011: n=145, Italy CLEAR 2013: n=84, the Netherlands and United Kingdom France 1998 (unpublished): n=170, France Holz 1993 (abstract only): n=58, United Kingdom Kaiser 1995: n=20, Switzerland LISA 2011: n=126, Austria Ma 2012: n=108, China Newsome 1988: n=174, United States Newsome 2008: n=80, United States Stur 1996: n=112, Austria VECAT 2002: n=1,204, Australia Veterans LAST 2004: n=90, United States Wang 2004: n=400, China</p>	<p>A. Average age: 66 to 75 years Median % female: 55% (2 trials recruited mostly males) Enrolled those with: Early AMD: 6 trials Range of AMD: 2 trials (including AREDS 2001) More severe AMD: 1 trial</p> <p>B. Average age: 69 to 75 years Median % female: 57% (1 trial recruited mostly males) Enrolled those with: Early AMD: 3 trials Range of AMD: 1 trial At risk for progression to advanced AMD: 1 trial (AREDS2 2013)</p> <p>C. Average age: 66 years % female: 56% Enrolled those from the general population (19% AMD, mostly early AMD)</p> <p>D. Average age: 65 to 74 years Median % female: 57% Enrolled those with: Early AMD: 2 trials Range of AMD: 2 trials (including AREDS 2001) Late stage AMD: 1 trial Neovascular AMD in one eye and drusen in the other: 1 trial</p>	11,162 (70.5% AREDS studies)	<p>A. Antioxidant multivitamin and mineral supplements (9 trials: AMDSG 1996, AREDS 2001, Bartlett 2007, Berrow 2013, CARMIS 2011, CARMA 2013, Kaiser 1995, Veterans LAST 2004, Wang 2004)</p> <p>B. Lutein and/or zeaxanthin (5 trials: AREDS2 2013, CLEAR 2013, LISA 2011, Ma 2012, Veterans LAST 2004)</p> <p>C. Vitamin E (1 trial: VECAT 2002)</p> <p>D. Zinc (6 trials: AREDS 2001, France 1998, Holz 1993, Newsome 1988, Newsome 2008, Stur 1996)</p> <p>E. Placebo or no treatment</p>

Appendix B Table 13. Systematic Review of Multivitamins

Author, year	Vision outcomes	Other outcomes	Adverse events	Quality
Evans 2017	<p>A vs. E, average followup 6 years Progression to late AMD (neovascular AMD, geographic atrophy, or both): 3 trials, N=2,445 people, OR 0.72 (95% CI 0.58 to 0.90) Progression to neovascular AMD: 1 trial, N=1,206 people, OR 0.62 (95% CI 0.47 to 0.82) Progression to geographic atrophy: 1 trial, N=1,206 people, OR 0.75 (95% CI 0.51 to 1.10) Progression to visual loss (loss of ≥ 3 lines on logMAR chart): 1 trial, N=1,791 people, OR 0.77 (95% CI 0.62 to 0.96) VA reported as continuous data (5 trials, N=595): pooled MD: 0.02 logMAR (95% CI -0.03 to 0.07), I²=38%</p> <p>B vs. E, average followup 5 years Progression to late AMD (neovascular AMD, geographic atrophy, or both): 1 trial, N=6,891 eyes, RR 0.94 (95% CI 0.87 to 1.01) Progression to neovascular AMD: 1 trial, N=6,891 eyes, RR 0.92 (95% CI 0.84 to 1.02) Progression to geographic atrophy: 1 trial, 6,891 eyes, RR 0.92 (95% CI 0.80 to 1.05) Progression to visual loss (loss of >3 lines on logMAR chart): 1 trial, 6,656 eyes, RR 0.98 (95% CI 0.91 to 1.05) Mean logMAR VA (3 trials, N=231): MD 0.00 logMAR (95% CI -0.05 to 0.05), I²=0%</p> <p>C vs. E, average followup 4 years Progression to late AMD (neovascular AMD, geographic atrophy, or both): 1 trial, N=998 people, RR 1.36 (95% CI 0.31 to 6.05) Progression to neovascular AMD: NR Progression to geographic atrophy: NR Progression to visual loss (loss of >3 lines on logMAR chart): 1 trial, 1,179 people, RR 1.04 (95% CI 0.74 to 1.47)</p> <p>D vs. E, average followup 6 years Progression to late AMD (neovascular AMD, geographic atrophy, or both): 3 trials, N=3,790 people, OR 0.83 (95% CI 0.70 to 0.98) Progression to neovascular AMD: 1 trial, N=2,442 people, OR 0.76 (95% CI 0.62 to 0.93) Progression to geographic atrophy: 1 trial, N=2,442 people, OR 0.84 (95% CI 0.64 to 1.10) Progression to visual loss (loss of >3 lines on logMAR chart): 2 trials, 3,791 people, RR 0.87 (95% CI 0.75 to 1.00) Stur 1996, CNV development: 9 vs. 5 Newsome 2008 analyzed zinc-monocysteine, 6 month followup: distance VA (number of letters read): +4 letters vs. -1 letter</p>	<p>A vs. E, average followup 2 years QoL (NEI-VFQ 25) mean change score (higher is better): 1 trial, N=110, 3.6 (95% CI 0.50 to 6.81) vs. -8.7 (95% CI -16.54 to -0.97), MD 12.0 (95% CI 4.24 to 20.36) CARMIS Piermarocchi 2001 study</p> <p>B vs. E, average followup 1 year QoL (NEI-VFQ 25) mean score (higher is better): 1 trial, N=108, MD 1.48 higher (-5.53 to 8.49) Ma 2012/Huang 2015 study</p> <p>C vs. E QoL: No data</p> <p>D vs. E QoL: No data</p>	<p>A vs. E Data from AREDS: SAEs: none Mortality: HR 0.87 (95% CI 0.60 to 1.25) Yellow skin: 8.3% vs 6.0%, p=0.008</p> <p>B vs. E Data from AREDS2: SAEs: none Mortality: HR 1.06 (95% CI 0.87 to 1.31)</p> <p>Data from LISA 2011: Withdrawal due to SAEs: 2 (unclear which group)</p> <p>C vs. E SAEs: none Withdrawal to AEs: 4 vs. 7 people Any AE: 91 vs. 83 people Ocular AE 105 vs. 90 people</p> <p>D vs. E Withdrawal due to gastrointestinal symptoms: 5/146 vs. 2/140 Copper-deficiency anaemia: none Anaemia (in AREDS trial): 13.2% vs. 10.2%, p=0.004 Hospital admissions due to genitourinary problems (in AREDS trial): 11.1% vs. 7.6%, p=0.0003</p>	Good

Abbreviations: AE = adverse event; AMD = age-related macular degeneration; AMDSG = AMDSG trial; AMED = Allied and Complementary Medicine Database; AREDS = Age-Related Eye Disease Studies; CARMA = CARMA trial; CARMIS = CARMIS trial; CI = confidence interval; CLEAR = CLEAR

Appendix B Table 13. Systematic Review of Multivitamins

trial; CNV = choroidal neovascularization; HR = hazard ratio; ISRCTN = International Standard Randomised Controlled Trial Number; LAST = LAST trial; LISA = LISA trial; logMAR = logarithmic minimum angle of resolution; MD = mean difference; NEI -VFQ = National Eye Institute Visual Functioning Questionnaire; NIH = National Institutes of Health; OR = odds ratio; QoL = quality of life; RCT = randomized controlled trial; RR = relative risk; SAEs = serious adverse events; VA = visual acuity; VECAT = VECAT trial; WHO = World Health Organization.

Appendix B Table 14. Systematic Review of Multivitamins, Quality Assessment

Author, year	"A priori" design provided?	Duplicate study selection and data abstraction?	Comprehensive literature search performed?	Searched for more than published studies?	List of included and excluded studies provided?	Characteristics of the included studies provided?	Scientific quality of included studies assessed and documented?	Study conclusions supported by the evidence?	Methods used to combine the findings of studies appropriate?	Likelihood of publication bias assessed?	Conflict of interest stated for systematic review or individual studies?	Quality
Evans, 2017	Yes	Yes Yes	Yes	Yes	Yes Yes	Yes	Yes Yes	Yes	Yes	No	Yes No	Good

Appendix B Table 15. Additional Trials of Multivitamins

Author, year study name	Study design	Country setting	Inclusion criteria	Randomized analyzed attrition	Intervention (n)	Baseline population/ study participants, including vision parameters	Duration of followup
Piatti 2020 GOAL group (Scientific Association of Italian Ophthalmologists operating in Eye Primary Care)	RCT	Italy 8 centers	Age 55-80 years, diagnosis of intermediate AMD, according to AREDS classification, presence of medium ($\geq 63\mu\text{m}$, $< 125\mu\text{m}$) and/or large ($\geq 125\mu\text{m}$) drusens and/or small aread of non-contral retinal atrophy in both eyes, BCVA for distance $\geq 20/32$ Snellen decimal (logMAR 0.2) and a minimum numbers of 43 letters read at the ETDRS chart, BCVA for near $\geq 20/32$ Snellen decimal (logMAR 0.2) at the MNREAD chart Exclude: presence myopias > 3 dioptrés or any other disorder of the macula and eye surgery in the 3 months prior to enrollment	Randomized: 80 Analyzed: 74 Attrition: 7.5% (74/80)	A. Nutritional supplement containing carotenoids (lutein 10 mg, astaxanthin 4 mg, zeaxanthin 2 mg) antioxidants (vitamin C 90 mg, vitamin E 30 mg, zinc 22.5 mg plus copper 1 mg) and omega-3 fatty acids (fish oil 500 mg, containing EPA 185 mg and DHA 140 mg), 1 tablet daily (n=48) B. Placebo (n=26)	A vs. B Mean age: 71.4 vs. 72.7 years % female: 64.6% vs. 76.9% Drusen type: 45.8% hard and 54.2% soft vs. 42.3% hard and 57.7% soft VA (ETDRS letter, mean): 49.4 vs. 47.6	2 years
Tao 2016	RCT	China Hospital	Age 60-83 years with dry AMD, no diabetes or HTN that may affect to retinal function; lens opacity and ocular media remained transparent; no family history of glaucoma, IOP normal and C/D ≤ 0.4 ; no high myopia, uveitis and retinal detachment	Randomized: 100 Other details NR	A. α -lipoic acid capsules, 0.2g daily (n=50) B. Placebo as vitamin C 1.0g daily (n=50)	A vs. B Mean age: 70.9 vs. 72.1 years % female: 48% vs. 44% Disease duration: 3.2 vs. 3.5 years BCVA (logMAR): 0.64 vs. 0.61 LVQOL: 73.5 vs. 74.3	3 months

Appendix B Table 15. Additional Trials of Multivitamins

Author, year study name	Vision-related outcomes	Other outcomes	Adverse events	Sponsor	Quality
Piatti 2020 GOAL group (Scientific Association of Italian Ophthalmologists operating in Eye Primary Care)	A vs. B AMD progression Retinography: worsened 2.1% (1/48) vs. 15.4% (4/26); stable or improved 97.9% (47/48) vs. 84.6% (22/26), p=0.05 Distance VA: worsened 14.6% (7/48) vs. 19.2% (5/26); stable or improved 85.4% (41/48) vs. 80.8% (21/26), p=0.74 Near VA: worsened 16.7% (8/48) vs. 34.6% (9/26); stable or improved 83.3% (40/48) vs. 65.4% (17/26), p=0.08 Combination of retinography, distance and near VA worsened: yes 0% (0/48) vs. 11.5% (3/26); no 100% (48/48) vs. 88.5% (23/26), p=0.04	NR	"No AEs were recorded"	No financial support received	Fair
Tao 2016	A vs. B BCVA (logMAR): 0.66 vs. 0.63, p=ns	A vs. B LVQOL (Chinese version, 0 to 125, higher is better): 82.6 vs. 72.8, p<0.05	NR	Science and Technology Development Planning of Shandong Province	Fair

Abbreviations: AE = adverse event; AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Studies; BCVA = best-corrected visual acuity; C/D = cup/disc; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; ETDRS = Early Treatment Diabetic Retinopathy Study; GOAL = Gruppo Oculisti Ambulatoriali Liberi – Scientific Association of Italian Ophthalmologists operating in Eye Primary Care; HTN = hypertension; IOP = intraocular pressure; logMAR = logarithmic minimum angle of resolution; LVQOL = low vision quality of life; NR = not reported; RCT = randomized controlled trial; VA = visual acuity.

Appendix B Table 16. Additional Trials of Multivitamins, Quality Assessment

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential or high?	People analyzed in the groups in which they were randomized?	Quality
Piatti, 2020	Randomized but method not described	Unclear	Yes, slightly more females in placebo group	Yes	Unclear	Unclear	Yes	Yes	No	Yes	Fair
Tao, 2016	Randomized but method not described	Unclear	Yes	Yes	Unclear, however researchers did not conduct the statistical analyses	Unclear	Yes	No	No	Yes	Fair

Appendix B Table 17. Trials of Multivitamins, Harms

Author, year	Intervention	N	Adverse effects
AMDSG Richer 1996 Part 2*	Multivitamin	71	1 allergic reaction (whole body rash) in multivitamin arm Diarrhea: 3 people in multivitamin arm Mean scores, antioxidant arm vs. placebo arm, 18 months: Diarrhea 0.12 vs. 0.06 Constipation: 0.21 vs. 0.17 Nausea/vomiting: 0.06 vs. 0.00 Dyspeptic symptoms: 0.06 vs. 0.06
AREDS Research Group, 2001* AREDS Report No. 8 Chew, 2013 AREDS Report No. 35*	Multivitamin and zinc vs. placebo	3,640	AREDS 2001 Report No. 8 Of nearly 100 analyses, only causes and conditions significantly different by treatment are presented (other details NR): Yellow skin, antioxidant vs. no antioxidant arms: 8.3% vs. 6.0%, p=0.008 Skin and subcutaneous tissue conditions, antioxidant vs. no antioxidant arms: 2.2% vs. 1.0%, p=0.03 Self-reported anemia, zinc vs. no zinc arms: 13.2% vs. 10.2%, p=0.04 Hospitalizations due to infections, antioxidant vs. no antioxidant arms: 1.6% vs. 0.8%, p=0.04 Hospitalizations due to genitourinary causes, zinc vs. no zinc arms: 7.5% vs. 4.9%, p=0.001 Hospitalizations for mild/moderate symptoms, zinc vs. no zinc arms: 9.7% vs. 7.8%, p=0.04 Hospitalizations for mild/moderate symptoms, antioxidant vs. no antioxidant arms: 7.4% vs. 10.1%, p=0.005 Circulatory AEs, antioxidant vs. no antioxidant arms: 0.3% vs. 0.8%, p=0.04 Circulatory AEs, zinc vs. no zinc arms: 0.9% vs. 0.3%, p=0.01 Chest pains, antioxidant vs. no antioxidant arms: 20.2% vs. 23.1%, p=0.03 Sex/gender: Hospitalizations due to genitourinary causes, zinc vs. no zinc: Males: 8.6% vs. 4.4%, p<0.01 Females: 6.7% vs. 5.3% AREDS, Chew 2013 Report No. 35 "No statistically significant increase in hospitalizations was associated with assignment to any of the AREDS supplements in the clinical trial during the 10-year followup in logistic regression analysis adjusted for age, sex, smoking status, and treatment." Details NR
AREDS2, 2013* JAMA 2013 309;(19): 2005-2015	Multivitamin and zinc Primary randomization: A. Lutein + zeaxanthin + EPA + DHA B. EPA + DHA C. Lutein + zeaxanthin D. Placebo **Those in the placebo group were also given the AREDS supplement either within or outside of the secondary	4,203	Primary randomization: No statistically significant in reported SAEs across groups A vs. B vs. C vs. D Participants with >1 SAE: 48.1% vs. 47.3% vs. 46.4% vs. 47.3% Cardiac disorders: 9.5% vs. 11.1% vs. 10.5% vs. 9.5% GI tract disorders: 5.7% vs. 5.4% vs. 6.6% vs. 7.5% Infections: 9.2% vs. 9.6% vs. 9.8% vs. 8.9% Neoplasms benign, malignant, and unspecified: 8.5% vs. 7.8% vs. 8.4% vs. 7.9% Nervous system disorders: 6.8% vs. 6.7% vs. 7.1% vs. 6.5% Respiratory tract, thoracic, and mediastinal disorders: 4.3% vs. 3.5% vs. 4.1% vs. 4.3%

Appendix B Table 17. Trials of Multivitamins, Harms

Author, year	Intervention	N	Adverse effects
	randomization for the 4 variations of the AREDS supplements; thus there is no true placebo group Secondary randomization: Those who consented to a second randomization were randomly assigned to: E. Standard AREDS F. AREDS with no beta-carotene G. AREDS with low dose zinc H. AREDS with no beta-carotene + low dose zinc Other Refused secondary randomization, of which: I. Received original AREDS J. Did not take AREDS		Incident lung neoplasm: 1.6% vs. 2.1% vs. 1.5% vs. 0.9% Secondary randomization/other: Excluding smokers, more lung cancers in beta carotene group than no beta carotene group: 2.0% (23) vs. 0.9% (11), p=0.04 E vs. F vs. G vs. H vs. I vs. J - No statistically significant in reported SAEs across groups Participants with >1 serious AE: 50.1% vs. 47.5% vs. 50.1% vs. 47.5% vs. 43.6% vs. 52.6% Cardiac disorders: 10.5% vs. 10.4% vs. 9.6% vs. 13% vs. 8.1% vs. 15.8% GI tract disorders: 5.9% vs. 6.4% vs. 5.4% vs. 6.9% vs. 6.5% vs. 5.3% Infections and infestations: 8.5% vs. 9% vs. 9.4% vs. 10.2% vs. 9.6% vs. 5.3% Neoplasms benign, malignant, and unspecified: 9.7% vs. 7.5% vs. 9% vs. 8.1% vs. 7.2% vs. 10.5% Nervous system disorders: 7.3% vs. 6.7% vs. 8% vs. 6.5% vs. 5.7% vs. 26.3% Respiratory tract, thoracic, and mediastinal disorders: 3.2% vs. 4.6% vs. 4.4% vs. 5.2% vs. 3% vs. 5.3% Incident lung neoplasm: 1.4% vs. 1.5% vs. 2% vs. 1.6% vs. 1.2% vs. 5.3% Note: smokers were not randomized to receive beta carotene; analyses of neoplasm and lung cancer include all participants regardless of smoking status
Bartlett 2007*	Multivitamin	25	Stated no AEs reported
Berrow 2013*	Multivitamin	14	Stated no withdrawals from treatment group
CARMA* Beatty 2013	Multivitamin	433	No data
CARMIS* Piermarocchi 2011	Multivitamin	145	Stated no significant systemic or ocular AEs related to the supplement Withdrawal due to AE: 6 in multivitamin arm vs. 1 in control arm Discontinued intervention due to AE: 7 in multivitamin arm vs. 4 in control arm
CLEAR* Murray 2013	Lutein	72	Discontinued due to medical reasons: 3 lutein arm vs. 1 placebo arm
France 1998*	Zinc	170	No data
Holz 1993*	Zinc	58	Stated that zinc was well tolerated
Kaiser 1995*	Multivitamin	20	Stated no AEs
LISA* Weigert 2011	Lutein	126	Withdrawal due to serious AEs: 2 (1 myocardial infarction and 1 developed CNV in the study eye) in lutein arm vs. 1 in placebo arm (CNV)
Ma 2012*	Lutein and zeaxanthin	108	Stated no AEs
Newsome 1988*	Zinc	151	Stated that AEs were minimal Withdrawal due to AEs: 1 (aggravated preexisting peptic ulcer symptoms) Gastrointestinal symptoms: 1
Newsome 2008*	Zinc mono-cysteine	80	Stated appeared to be well tolerated Gastrointestinal symptoms: 1 in treatment arm
Piatti 2020	Nutritional supplement containing carotenoids (lutein 10 mg, astaxanthin 4 mg, zeaxanthin 2 mg) antioxidants (vitamin C 90 mg, vitamin E 30 mg, zinc 22.5 mg plus copper 1 mg) and omega-3 fatty acids	80	"No AEs were recorded"

Appendix B Table 17. Trials of Multivitamins, Harms

Author, year	Intervention	N	Adverse effects
	(fish oil 500 mg, containing EPA 185 mg and DHA 140 mg), 1 tablet daily		
Stur 1996*	Zinc	112	Withdrawal due to gastrointestinal symptoms: 4 in zinc arm vs. 2 in placebo arm
VECAT* Taylor 2002	Vitamin E	1,193	Withdrawal or discontinued intervention due to AE: 16 in vitamin E arm vs. 17 in control arm Mortality: 11 in vitamin E arm vs. 7 in control arm Serious AEs: none At least 1 AE: 678 total (NR by arm) No significant difference between overall number and type of AE between the arms, p=0.97 AEs potentially related to the use of study capsules: 91 in vitamin E arms vs. 83 in control arm, p=0.49 Ophthalmic AEs: 105 in vitamin E arm vs. 90 in control arm, p=0.23
Tao 2016	α-lipoic acid	100	NR
Wang 2004*	Multivitamin and zinc	400	NR

* Studies included in Evans 2017 Cochrane review.

Abbreviations: AEs = adverse events; AMDSG = AMDSG trial; AREDS = Age-Related Eye Disease Studies; CARMA = CARMA trial; CARMIS = CARMIS trial; CLEAR = CLEAR trial; CNV = choroidal neovascularization; CV = cardiovascular; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; LAST = LAST trial; LISA = LISA trial; NR = not reported; SAEs = serious adverse events; VECAT = VECAT trial.