Association between vision impairment and mortality: a systematic review and meta-analysis

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Summary

Background The number of individuals with vision impairment worldwide is increasing because of an ageing population. We aimed to systematically identify studies describing the association between vision impairment and mortality, and to assess the association between vision impairment and all-cause mortality.

Methods For this systematic review and meta-analysis, we searched MEDLINE (Ovid), Embase, and Global Health database on Feb 1, 2020, for studies published in English between database inception and Feb 1, 2020. We included prospective and retrospective cohort studies that measured the association between vision impairment and all-cause mortality in people aged 40 years or older who were followed up for 1 year or more. In a protocol amendment, we also included randomised controlled trials that met the same criteria as for cohort studies, in which the association between visual impairment and mortality was independent of the study intervention. Studies that did not report age-adjusted mortality data, or that focused only on populations with specific health conditions were excluded. Two reviewers independently assessed study eligibility, extracted the data, and assessed risk of bias. We graded the overall certainty of the evidence using the Grading of Recommendations, Assessment, Development and Evaluations framework. We did a random-effects meta-analysis to calculate pooled maximally adjusted hazard ratios (HRs) for all-cause mortality for individuals with a visual acuity of <6/12 versus those with ≥6/12; <6/18 versus those with ≥6/18; <6/60 versus those with ≥6/18; and <6/60 versus those with ≥6/60.

Findings Our searches identified 3845 articles, of which 28 studies, representing 30 cohorts (446 088 participants) from 12 countries, were included in the systematic review. The meta-analysis included 17 studies, representing 18 cohorts (47 998 participants). There was variability in the methods used to assess and report vision impairment. Pooled HRs for all-cause mortality were 1.29 (95% CI 1.20–1.39) for visual acuity <6/12 versus ≥6/12, with low heterogeneity between studies (I²=0.0%); 1.43 (1.22–1.68) for visual acuity <6/18 versus ≥6/18, with low heterogeneity between studies (I²=0.0%); 1.89 (1.45–2.47) for visual acuity <6/60 versus ≥6/18 (n=1); and 1.02 (0.79–1.32) for visual acuity <6/60 versus ≥6/60 (n=2; I²=0.0%). Three studies received an assessment of low risk of bias across all six domains, and six studies had a high risk of bias in one or more domains. Effect sizes were greater for studies that used best-corrected visual acuity compared with those that used presenting visual acuity as the vision assessment method (p=0.0055), but the effect sizes did not vary in terms of risk of bias, study design, or participant-level factors (ie, age). We judged the evidence to be of moderate certainty.

Interpretation The hazard for all-cause mortality was higher in people with vision impairment compared with those that had normal vision or mild vision impairment, and the magnitude of this effect increased with more severe vision impairment. These findings have implications for promoting healthy longevity and achieving the Sustainable Development Goals.

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Introduction Over half a billion people are blind or have distance vision impairment worldwide.1 Blindness and vision impairment are most common among adults aged 50 years and older, who account for more than 80% of people with vision loss.2 As populations continue to age, the prevalence of vision impairment and blindness are projected to more than double over the next 30 years. The impacts of vision impairment and blindness are wide-reaching, including an increased risk of falls, cognitive impairment and dementia, depression, disability, and loss of independence.2,3 Some studies have also reported that vision impairment and blindness are associated with an increased risk of mortality.4

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In a previous meta-analysis, Zhang and colleagues\(^1\) examined 29 studies that measured the association between vision impairment and mortality. Among these studies, 15 used objective measures of vision (eg, visual acuity), whereas others relied on self-reported visual difficulty, or vision impairment defined by International Classification of Diseases (ICD) codes. The risk of bias in these studies and the overall quality of evidence was not assessed.\(^1\) Since this meta-analysis was published in 2016, several additional primary studies have been published,\(^5\)\(^6\) including those done in previously under-represented regions, such as sub-Saharan Africa\(^5\) and east Asia.\(^6\)

An improved understanding of the association between vision impairment and mortality is needed to inform public policy, public health planning, and allocation of limited health-care resources. As part of The Lancet Global Health Commission on Global Eye Health,\(^7\) we...
Methods

Search strategy and selection criteria
In this systematic review and meta-analysis, we searched MEDLINE (Ovid), Embase, and Global Health database on Feb 1, 2020, for studies published in English between database inception and Feb 1, 2020. We included prospective and retrospective cohort studies that measured the association between vision impairment and all-cause mortality in people aged 40 years or older, who were followed up for 1 year or more. In a protocol amendment, we included randomised controlled trials (RCTs), as long as the reported association between vision impairment and mortality was independent of the study intervention; we also included RCTs and cohort studies with participants younger than 40 years if more than 50% of participants were aged 40 years or older. We assessed the effect of these protocol amendments on effect estimates in meta-regression analyses. Conference abstracts and grey literature were not included. We identified additional studies by searching the reference lists of included studies. The searches were done by an information specialist (IG), and the search strategy and full list of search terms used are provided in the appendix (pp 2–5).

We intended to include studies in which vision was assessed by use of any objective clinical measure of vision and in which age-adjusted all-cause mortality was reported. We only included studies in the meta-analysis that assessed visual acuity, as few studies reported associations with other measures of vision (eg, contrast sensitivity or visual fields). In studies that used best-corrected visual acuity and presenting visual acuity as vision assessment methods, data on best-corrected visual acuity were included in the primary analysis. Studies that did not report age-adjusted mortality, or that focused only on populations with specific health conditions (eg, diabetes or stroke) were excluded, as in such cases, age and systemic disease might have a strong confounding effect.

The internet-based systematic review management software, Covidence (Veritas Health Innovation, Melbourne, VIC, Australia), was used to screen titles and abstracts, assess full-text articles, and extract summary estimates from included studies. All titles, abstracts, and full-text articles were screened independently by pairs of investigators (one of JREh, JR, and JREv paired with one of HB, CNL, JHZ, or WW). Disagreements were resolved through discussion and adjudication by a third investigator (JREh, JR, or JREv), as needed.

This study was done as part of The Lancet Global Health Commission on Global Eye Health. The complete study protocol was registered prospectively at the Open Science Framework Registries, and has been published previously. Amendments to the initial study protocol are noted herein. We used the PROGRESS prognosis research strategy to develop the protocol for this study, which is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (appendix pp 6–7).

Data analysis
The following data were extracted from each publication: study setting; study timing; study design; sample size; age, gender, and ethnicity of study participants; follow-up time; definition of vision impairment; methods and eyes used for vision assessment; methods of mortality assessment; statistical modelling approach; and effect size estimates. Three pairs of investigators (JREh and CNL, JR and JHZ, and JREv and HB) independently extracted data from each article, guided by the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies framework. Disagreements were resolved through discussion and adjudication by a third investigator (JREh, JR, or JREv), as needed. When duplicate data were available from multiple published studies, preference was given to the study with the longest follow-up. Many studies reported results from models with different combinations of covariates. When estimates were reported with more than one level of adjustment, we extracted two estimates: (1) the age-adjusted estimate with the fewest additional covariates (minimally adjusted); and (2) the age-adjusted estimate with the greatest number of additional covariates (maximally adjusted). When multiple publications contained data from a single cohort, data were extracted from the publication with the longest follow-up. When data on multiple cohorts were presented in a single publication, each cohort was separately eligible for inclusion.

The risk of bias in included studies was assessed independently by three pairs of investigators (JREh and CNL, JR and JHZ, and JREv and HB) using the Quality in Prognostic Studies (QUIPS) tool. The following domains were assessed: study participation, attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting. Risk of bias was defined as high if a study received a high rating in one or more domains; low if it received a low rating in all six domains; or moderate if it did not meet criteria for low or high risk or bias. Disagreements on risk of bias ratings were resolved through discussion and adjudication by a third investigator (JREh, JR, or JREv).

We classified vision impairment according to WHO reporting standards: mild vision impairment (visual acuity <6/12 to 6/18); moderate vision impairment (<6/18 to 6/60); and severe vision impairment or blindness (<6/60). We compared the following visual
acuity thresholds in the meta-analysis: (1) <6/12 versus ≥6/12; (2) <6/18 versus ≥6/18; (3) <6/60 versus ≥6/18; and (4) <6/60 versus ≥6/60. Note that some studies classified visual acuities at the category threshold as vision impairment, whereas others did not (eg, ≤6/12 vs 6/12).

We did a random-effects meta-analysis to generate a pooled effect estimate, reported as the hazard ratio (HR) with 95% CIs, for the association between vision impairment and age-adjusted, all-cause mortality. Between-study heterogeneity was assessed with I² and τ² statistics. The primary analysis used maximally adjusted estimates, and the sensitivity analysis used minimally adjusted estimates. For studies in which only one estimate was available, the same estimate was used in both the maximally adjusted and minimally adjusted models.

We did meta-regression analyses to test whether effect estimates varied by the following factors: risk of bias, type of visual acuity chart, analysis of better-eye data (compared with other definitions), the use of best-corrected visual acuity or presenting visual acuity as the vision assessment method, follow-up duration, a lower age limit (ie, participants aged <50 years vs those aged ≥50 years), and study design. We only did meta-regression analyses for studies that reported on the association between mortality and vision impairment, defined as a visual acuity of <6/12, as there were too few studies to do meta-regression analyses for other vision impairment categories. The results are not reported by Global Burden of Disease Study super-region as planned because all studies with a visual acuity <6/12 group were done in high-income countries. We assessed publication bias using Egger’s test (threshold for significance p<0·05) and by inspection of funnel plots. All analyses were done with Stata software, version 16.0.

Two investigators (JREh and JREv) graded the overall certainty of the evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework, modified for prognostic studies. This instrument is used to rate the certainty of evidence by considering risk of bias, imprecision, inconsistency, indirectness, and publication bias.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 3845 articles through electronic database searches. After removing duplicate references, we screened the titles and abstracts of 2670 articles. Of these, we identified 76 unique studies in 92 articles for full-text review, during which 48 studies were excluded, leaving 28 studies5–10,19–40 that met the inclusion criteria. Two of the studies each included two distinct cohorts; therefore, these 28 studies comprised 30 distinct cohorts (446088 participants) from 12 countries. 25 were observational cohort studies,6,8–10,21–40 and three were RCTs7,19,20 reporting an association between vision impairment and mortality independent of the trial interventions.

The characteristics of each cohort are reported in table 1. The global distribution of the included cohorts is shown in figure 2; there were no cohorts from eastern Europe, Latin America, the Caribbean, north Africa, or the Pacific islands.

Studies collected data between the 1970s and 2012. The findings from six cohorts had been published since 2015.25–28 The duration of follow-up among included studies ranged from 17 months to 210 months, with a mean of 103·3 (SD 46·4) months. Sample sizes ranged from 193 participants in Finland21 to 359984 participants in Korea.24 24 cohorts contained an approximately equal number of male and female participants. However, the study by Pedula and colleagues22 included female participants only, and five other cohorts comprised less than 40% male participants.10,19,21,23 None of the included studies had less than 40% female participants, although one study did not report on the gender distribution of participants.28
| Studies using the same cohort | Country | Sample size | Age, years | Ethnic group | Study design | Baseline assessment period | Mean follow-up, months | Visual acuity assessment instrument | Vision assessment method (eye) | Vision impairment definition | Mortality assessment method |
|--------------------------------|---------|-------------|------------|--------------|-------------|---------------------------|-----------------------|-----------------------------|--------------------------------|----------------------------|-------------------------------|
| Agrawal et al (2011) | India | 1,422 (687 [48%] men and 735 [52%] women) | ≥60 | NR | Cohort | 2008-09 | 17 | Snellen chart | PVA (better eye) | <6/60 | Death registry maintained by local health workers |
| Anstey et al (2001) | Australia | 1,947 (751 [52%] men and 908 [47%] women) | ≥70 | NR | Cohort | 1992-93 | 72 | Snellen chart | BOCA (eye NR) | Various categories | Follow-up with participants and death certificates |
| Buch et al (2005) | Denmark | 946 (462 [49%] men and 484 [51%] women) | 60-80 | NR | Cohort | 1986-88 | 168 | Snellen chart | BOCA (better eye) | ≤6/12 | National death registry |
| Clemens et al (2004) | USA | 4,753 (2,099 [44%] men and 2,654 [56%] women) | 55-81 | 4,546 (95%) white and 207 (5%) other | RCT | 1992-98 | 78 | ETDRS chart | BCVA (either eye) | <6/12 | Death certificates and hospital records |
| Crewe et al (2015) | Australia | 3,623 (1,250 [39%] men and 2,373 [61%] women) | ≥65 | 3,233 (94%) non-Indigenous Australians, 15 (<1%) Indigenous Australians, and 208 (6%) unknown | Cohort | 2003-10 | 123 | NR | BCVA (better eye) | <6/60 | National death registry |
| Fishe et al (2014) | Iceland | 4,926 (2,121 [43%] men and 2,805 [57%] women) | 66-96 | NR | Cohort | 2002-06 | 64 | Nidek ARK 760 | PVA (better eye) | <6/12 | National death registry |
| Forong et al (2008) | Singapore | 1,275 (55% [45%] men and 672 [55%] women) | 40-79 | NR | Cohort | 1997-98 | 80 | logMAR | BCVA (better eye) | <6/12 | National death registry |
| Freeman et al (2005) | USA | 1,917 (836 [43%] men and 1,125 [58%] women) | 65-84 | 497 (25%) African American and 1,454 (74%) white | Cohort | 1993-2003 | 118 | ETDRS chart | BCVA (eye NR) | ≤6/12 | National death registry |
| Jacob et al (2005) | Israel | 452 (245 [54%] men and 207 [46%] women) | 70 | NR | Cohort | 1990 | 96 | Snellen equivalent | BCVA (better eye) | ≤6/12 | National death registry |
| Karpa et al (2009) | Australia | 3,954 (1,569 [43%] men, 2,954 [52%] women, and 31 [1%] NR) | 49-97 | NR | Cohort | 1991 and 1993 | 156 | logMAR | BCVA (better eye) | ≤6/12 | National death registry |
| Khanna et al (2013) | India | 4,188 (1,964 [42%] men and 2,224 [58%] women) | 30-70 | NR | Cohort | 1996-2000 | 132 | logMAR | PVA (eye NR) | ≤6/18, ≤6/60 | Key informants |
| Kim et al (2019) | South Korea | 359,984 (195,052 [54%] men and 164,932 [46%] women) | ≥40 | NR | Cohort | 2009-10 | 48 | NR | BOCA (various) | ≤6/30, ≤6/300 | National death registry |
| Knudtson et al (2006) | USA | 4,873 (42% men and 58% women) | 43-84 | 99% white and 1% NR | Cohort | 1987-88 | 158 | ETDRS chart | BCVA (better eye) | ≤6/12 | National death registry and follow-up with participants |
| Kulma et al (2008) | Finland | 223 (80 [36%] men and 143 [64%] women) | 75 | Finnish | Cohort | 1989-90 | 106 | Landolt C ring | PVA (better eye) | Various categories | National death registry and follow-up with participants |
| Kulma et al (2008) | Finland | 193 (56 [29%] men and 137 [71%] women) | 80 | Finnish | Cohort | 1989-90 | 89 | Landolt C ring | PVA (better eye) | Various categories | National death registry and follow-up with participants |
| Kuper et al (2013) | Kenya | 3,441 (1,666 [48%] men and 1,775 [52%] women) | ≥50 | Kikuyu and Kalenjin | Cohort | 2007-14 | 72 | logMAR | PVA (better eye) | Various categories | Key informants |
| Lee et al (2003) | USA | 245 (109 [44%] men and 136 [56%] women) | 25-74 | African American | Cohort | 1974-75 | 210 | Sloan chart | PVA (binocular) | ≤6/12 | National death registry, death certificates, hospital records, insurance records, key informants, and follow-up with participants |

(Table 1 continues on next page)
### Table 1: Summary of included cohorts

| Study                              | Country               | Sample size | Age, years | Ethnic group | Study design | Mean follow-up, months | Visual acuity assessment instrument | Vision assessment method (eye) | Vision impairment definition | Mortality assessment method |
|------------------------------------|-----------------------|-------------|------------|--------------|--------------|------------------------|-----------------------------------|--------------------------------|-------------------------------|-----------------------------|
| Lee et al (2003)                   | USA                   | 2571 (1163 [45%] men and 1408 [55%] women) | 25–74      | Non-Hispanic white | Cohort, 1974–75 | 210 | Sloan chart | PVA (binocular) | <6/12 | National death registry, hospital records and key informants |
| Li et al (2011)                    | China                 | 527 (233 [44%] men and 294 [56%] women) | 50–90      | NR           | Cohort, 1999–2003 | 316 | National death registry, hospital records and key informants | PVA (binocular) | <6/12, <6/20 | Follow-up with participants and death certificates |
| Liao et al (2019)                  | China                 | 569 (260 [46%] men and 309 [54%] women) | 25–74      | Non-Hispanic white | Cohort, 1974–75 | 210 | Sloan chart | PVA (binocular) | <6/12 | National death registry, hospital records and key informants |
| Loprinzi et al (2016)              | USA                   | 900 (414 [46%] men and 486 [54%] women) | 58–102     | Non-Hispanic white, non-Hispanic Black, and other | Cohort, 1992–95 | 120 | Bailey-Lovie chart | PVA (binocular) | ≤6/12 | Follow-up with participants and death certificates |
| Ng et al (2018)                    | USA                   | 1658 (800 [48%] men and 858 [52%] women) | 40–85      | Non-Hispanic white, non-Hispanic Black, Mexican American, and other | Cohort, 2003–04 | 92 | Nidek ARK 760 | BCVA (better eye) | ≤6/12 | National death registry |
| Papudesu et al (2018)              | USA                   | 4203 (1816 [43%] men and 2387 [57%] women) | 50–80      | Non-Hispanic white and other | RCT, 2006–08 | 60 | ETDRS chart | BCVA (left eye) | NR | National death registry, hospital records and key informants |
| Siantar et al (2015)               | Singapore             | 3273 (1573 [48%] men and 1700 [52%] women) | 40–79      | Malay | Cohort, 2004–07 | 87 | logMAR | logMAR | NT | National death registry, hospital records and key informants |
| Siantar et al (2015)               | UK                    | 875 (495 [57%] men and 380 [43%] women) | 25–75      | Non-Hispanic white and other | Cohort, 1992–95 | 60 | Snellen Tumbling E chart | PVA (binocular) | ≤6/12 | Follow-up with participants and death certificates |
| Thompson et al (2018)              | UK                    | 469 (259 [55%] men and 210 [45%] women) | 58–102     | NR | Cohort, 1981–87 | 60 | Snellen Tumbling E chart | PVA (binocular) | ≤6/12 | National death registry, hospital records and key informants |
| Xu et al (2019)                    | China                 | 4439 (1948 [44%] men and 2591 [56%] women) | 50–98      | Han Chinese | Cohort, 2001–13 | 120 | Snellen Tumbling E chart | PVA (binocular) | ≤6/12 | National death registry, hospital records and key informants |
| Yang et al (2014)                  | China                 | 499 (270 [54%] men and 229 [46%] women) | 58–102     | Han, other | Cohort, 1992–95 | 60 | Snellen Tumbling E chart | PVA (binocular) | ≤6/12 | Follow-up with participants and death certificates |

**ART**-administered or knee to war. **ROV**-best correction visual acuity. **ETDRS**-Early Treatment Diabetic Retinopathy Study. **logMAR**-logarithm of the minimum angle of resolution.

**NA**-not applicable. **NR**-not reported.
20 publications reported the HR as an effect estimate. Eight publications reported odds ratios or risk ratios of death for a given follow-up period. Given the high mortality rates in most cohorts, these estimates of effect size could not be considered as equivalent. Thus, meta-analyses were done only with studies reporting HRs or incident rate ratios.

Measures of vision other than visual acuity were not commonly used. Several studies measured visual fields,6,23 contrast sensitivity,22,25 colour vision,23 and stereopsis.25 In this subset of studies, contrast sensitivity impairment, peripheral field loss, and stereoscopic vision impairment were all significantly associated with an increased hazard for mortality in adjusted models. However, because of the small number of studies that assessed vision using these tests, only visual acuity was considered in this report.

Studies used a wide variety of instruments to assess visual acuity. The most commonly used vision charts were logarithm of the minimum angle of resolution (n=6),5,26–30 Snellen charts (n=5),24,31–34 and Early Treatment Diabetic Retinopathy Study charts (n=5),7,20,35–37 whereas two studies did not specify the instrument used.6,23 There was also considerable heterogeneity in the methods used to define vision impairment. 15 (54%) studies used best-corrected visual acuity to define vision impairment, and 17 (61%) studies defined vision impairment based on visual acuity in the better-seeing eye.

Definitions of vision impairment also varied between studies. Two studies reported the association between mortality and a continuous measure of visual acuity.7,23 Six other studies (comprising seven cohorts) compared a reference group of participants with good vision with groups of participants with various non-overlapping vision impairment categories.5,19,21,24,26,31 The remaining studies compared participants with visual acuity better than and worse than one or more visual acuity thresholds.

Studies used various strategies to assess mortality, and were included regardless of the methods used because official death registries might not have been available or provided high-quality data in many low-income and middle-income countries (LMICs).57 Most studies (n=24) searched official vital records, with some (n=12) also relying on other methods, including following up with participants, key informants, or both.

The pooled maximally adjusted HRs for mortality in adults with vision impairment compared with those who had better vision are shown in figure 3. The 18 cohorts included in the meta-analysis comprised 47,998 participants. The remaining 12 cohorts identified in the systematic review were not included in the meta-analysis for one or more of the following reasons: they used a vision impairment threshold that could not be aggregated with other studies;6 they reported results per unit difference in visual acuity;32,37 they reported measures of effect that could not be pooled with HRs;5,19,21,24,26,31–33,35 or they compared a reference category of participants with good vision to participants with various non-overlapping vision impairment categories.5,7,20,21,24,26,31,35 The associations between vision impairment and mortality among these 12 cohorts are shown in table 2.

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A total of 14 studies (comprising 15 cohorts) compared the hazard for mortality in participants with a visual acuity of <6/12 versus those with a visual acuity of ≥6/12; the adjusted HR estimate for mortality was 1·29 (95% CI 1·20–1·39) and heterogeneity between studies was low.
suggesting a consistent effect across studies (figure 3). Two studies compared the hazard for mortality among participants with a visual acuity <6/18 versus those with a visual acuity of ≥6/18; the adjusted estimated HR for mortality was 1.43 (1.22–1.68) and heterogeneity between studies was low ($\tau^2=0.00$, $I^2=0.00\%$). Only one study compared the hazard for mortality in participants with a visual acuity of <6/60 versus those with a visual acuity of ≥6/18, with a HR for mortality of 1.89 (1.45–2.47).

The pooled minimally adjusted HR for mortality among participants with a visual acuity of <6/12 versus those with a visual acuity of ≥6/12 is shown in the appendix (p 8). In this analysis, the pooled minimally adjusted HR for mortality was 1.41 (95% CI 1.29–1.53).

For risk of bias assessment using the QUIPS tool, 16 only three studies received an assessment of low risk of bias across all six domains (figure 4). 29, 30, 35 Six studies were assessed as having a high risk of bias in one or more domains. 6, 9, 23, 24, 26, 31

Funnel plots were reviewed for studies comparing all-cause mortality in participants with a visual acuity of <6/12 with those that had a visual acuity of ≥6/12, and no evidence of publication bias was identified (p=0.63; appendix p 9). Meta-regression analysis of studies comparing all-cause mortality between these two groups of participants revealed no evidence that the estimated effect size differed by risk of bias, the type of vision

| Vision impairment | No vision impairment | Follow-up (months) | Hazard ratio (95% CI) |
|-------------------|---------------------|--------------------|----------------------|
| <6/12 vs ≥6/12    |                      |                    |                      |
| Bucht et al (2005)39 | 25/NA               | 168                | 1.17 (0.78–1.75)     |
| Clemons et al (2004)30 | 158/813            | 78                 | 1.36 (1.12–1.65)     |
| Fisher et al (2014)35 | 79/455              | 64                 | 0.93 (0.72–1.20)     |
| Foong et al (2008)37 | 46/213              | 80                 | 2.70 (1.36–5.35)     |
| Karpa et al (2009)36 | 273/399             | 156                | 1.29 (1.09–1.52)     |
| Knudson et al (2006)34 | 190/254             | 158                | 1.51 (1.28–1.75)     |
| Lee et al (2003)39 (African American) | 8/16           | 210                | 0.96 (0.62–1.48)     |
| Lee et al (2003)39 (non-Hispanic white people) | 35/96          | 210                | 1.14 (0.95–1.37)     |
| Liu et al (2019)31 | 149/272             | 119                | 1.37 (1.08–1.74)     |
| Loprinzi et al (2016)4 | 14/27              | 92                 | 1.17 (0.63–2.16)     |
| Lott et al (2010)35 | 102/134             | 120                | 1.27 (0.98–1.65)     |
| Ng et al (2018)39 | 156/322             | 120                | 1.40 (1.16–1.69)     |
| Papadieou et al (2018)26 | 31/227            | 60                 | 1.57 (1.07–2.31)     |
| Pedula et al (2006)32 | 1050/205           | 144                | 1.19 (1.04–1.36)     |
| Santar et al (2015)36 | 121/360            | 87                 | 1.46 (1.14–1.87)     |
| Heterogeneity $\tau^2=0.01$, $I^2=31.46\%$ |

| Visual acuity <6/18 vs ≥6/18 |                      |                    |                      |
| Khanna et al (2013)30 | 367/987              | 132                | 1.42 (1.19–1.70)     |
| Lott et al (2010)35 | 38/47                | 120                | 1.49 (1.05–2.12)     |
| Heterogeneity $\tau^2=0.00$, $I^2=0.00\%$ |

| Visual acuity <6/60 vs ≥6/18 |                      |                    |                      |
| Khanna et al (2013)30 | 105/206              | 132                | 1.89 (1.45–2.47)     |
| Heterogeneity $\tau^2=0.00$, $I^2=0.00\%$ |

| Visual acuity <6/60 vs ≥6/60 |                      |                    |                      |
| Agrawal et al (2011)34 | 15/134               | 17                 | 0.75 (0.41–1.38)     |
| Crewe et al (2015)35 | 577/1726             | 123                | 1.08 (0.96–1.22)     |
| Heterogeneity $\tau^2=0.02$, $I^2=25.04\%$ |

Figure 3: Random-effects meta-analysis results
For each study, the number of participants who died out of the total number of participants in the study is shown. Data are the maximally adjusted pooled hazard ratios of mortality in adults with mild vision impairment or worse (visual acuity <6/12) versus those with a visual acuity of ≥6/12, moderate vision impairment or worse (visual acuity <6/18) versus those with a visual acuity of ≥6/18, and severe vision impairment or blindness (visual acuity <6/60) versus those with a visual acuity of ≥6/18 and ≥6/60. NA=not applicable.

($\tau^2=0.01$, $I^2=31.46\%$), suggesting a consistent effect across studies (figure 3). Two studies compared the hazard for mortality among participants with a visual acuity <6/18 versus those with a visual acuity of ≥6/18; the adjusted estimated HR for mortality was 1.43 (1.22–1.68) and heterogeneity between studies was low ($\tau^2=0.00$, $I^2=0.00\%$). Only one study compared the hazard for mortality in participants with a visual acuity of <6/60 versus those with a visual acuity of ≥6/18, with a HR for mortality of 1.89 (1.45–2.47). Two studies compared the hazard for mortality in participants with a visual acuity of <6/60 versus those with a visual acuity of ≥6/60; the adjusted pooled HR for mortality was 1.02 (0.79–1.32; $\tau^2=0.02$, $I^2=25.04\%$).

The pooled minimally adjusted HR for mortality among participants with a visual acuity of <6/12 versus those with a visual acuity of ≥6/12 is shown in the appendix (p 8). In this analysis, the pooled minimally adjusted HR for mortality was 1.41 (95% CI 1.29–1.53).

For risk of bias assessment using the QUIPS tool, 16 only three studies received an assessment of low risk of bias across all six domains (figure 4). 29, 30, 35 Six studies were assessed as having a high risk of bias in one or more domains. 6, 9, 23, 24, 26, 31

Funnel plots were reviewed for studies comparing all-cause mortality in participants with a visual acuity of <6/12 with those that had a visual acuity of ≥6/12, and no evidence of publication bias was identified (p=0.63; appendix p 9). Meta-regression analysis of studies comparing all-cause mortality between these two groups of participants revealed no evidence that the estimated effect size differed by risk of bias, the type of vision
Articles

The table shows effect estimates of studies that were excluded from meta-analysis, with reasons for exclusion and definitions of vision impairment. BCVA=best-corrected visual acuity. HR=hazard ratio. NA=not applicable. NR=not reported. OR=odds ratio. PVA=presenting visual acuity. RR=risk ratio. *All estimates are, at minimum, adjusted for age.

Table 2: Results of studies not included in the meta-analysis

| Reason for exclusion from the meta-analysis | Vision impairment definition (vision assessment method, eye) | Comparison group | Minimally adjusted effect estimates (95% CI)* | Maximally adjusted effect estimates (95% CI) |
|--------------------------------------------|----------------------------------------------------------|----------------|-----------------------------------------------|---------------------------------------------|
| Anstey et al (2001)* | Categorical analysis | 6/9 (BCVA, eye NR); 6/12 (BCVA, eye NR); and 6/18 to 6/60 (BCVA, eye NR) | 6/6 | 6/9, RR 0.95 (0.67–1.33); 6/12, 1.16 (0.84–1.59); and 6/18 to 6/60, 1.10 (0.80–1.53) | 6/9, RR 0.89 (0.63–1.25); 6/12, 1.10 (0.80–1.52); and 6/18 to 6/60, 1.01 (0.72–1.39) |
| Freeman et al (2005)* | Effect estimate per unit change in visual acuity | Mild vision loss, 2–3 lines (PVA, eye NR); moderate vision loss, ≥3 lines (PVA, eye NR); and vision gain, ≥2 lines (PVA, eye NR) | No change in visual acuity | Mild vision loss, HR 0.92 (0.61–1.37); moderate vision loss, 2.25 (1.43–3.46); and vision gain, HR 0.47 (0.23–0.96) | Mild vision loss, HR 0.90 (0.61–1.36); moderate vision loss, 2.26 (1.45–3.52); and vision gain, 0.47 (0.23–0.95) |
| Jacobs et al (2005)* | Did not report HRs | ≤6/12 (BCVA, better eye) | NA | OR 2.84 (1.48–5.46) | |
| Kim et al (2019)* | Non-standard vision impairment thresholds | Mild vision loss, 6/30 to 6/100 (BCVA, better eye) or ≤6/300 (BCVA, worse eye); and severe vision loss, ≤6/300 (BCVA, better eye) | ≥6/30 | Mild vision loss, HR 1.17 (0.81–1.69); and severe vision loss, 1.90 (1.08–3.35) | Mild vision loss, HR 1.16 (0.81–1.67); and severe vision loss, 1.87 (1.05–3.29) |
| Kolmala et al (2008)* | Categorical analysis 75-year-old cohort | ≤6/12 to ≤6/18 (PVA, better eye); and ≥6/12 (PVA, better eye) | ≥6/12 | ≤6/12 to ≤6/18, HR 1.18 (0.92–1.53); and ≥6/12, 1.01 (0.80–1.26) | ≤6/12 to ≤6/18, HR 1.18 (0.92–1.53); and ≥6/12, 1.01 (0.80–1.26) |
| Kolmala et al (2008)* | Categorical analysis 80-year-old cohort | ≤6/12 to ≤6/18 (PVA, better eye); and ≥6/18 (PVA, better eye) | ≥6/12 | ≤6/12 to ≤6/18, HR 1.12 (0.74–1.72); and ≥6/18, 0.92 (0.47–1.78) | ≤6/12 to ≤6/18, HR 0.77 (0.49–1.26); and ≥6/18, 0.75 (0.33–1.67) |
| Kuper et al (2019)* | Categorical analysis and did not report HRs | ≤6/12 to ≤6/18 (PVA, better eye); and ≥6/18 to ≥6/60 (PVA, better eye) | ≥6/12 | ≤6/12 to ≤6/18, RR 0.92 (0.57–1.50); and ≥6/18 to ≥6/60, 1.75 (1.28–2.40); and ≥6/60, 1.98 (1.04–3.80) | ≤6/12 to ≤6/18, RR 0.92 (0.57–1.50); and ≥6/18 to ≥6/60, 1.75 (1.28–2.40); and ≥6/60, 1.98 (1.04–3.80) |
| Li et al (2011)* | Categorical analysis and did not report HRs | ≤6/18 to ≥3/60 (BCVA, better eye); and ≥3/60 (BCVA, better eye) | ≥6/18 | ≤6/18 to ≥3/60, OR 3.1 (1.5–6.4); and ≥3/60, 1.46 (2.1–3.7) | ≤6/18 to ≥3/60, OR 3.1 (1.5–6.4); and ≥3/60, 1.46 (2.1–3.7) |
| Taylor et al (2000)* | Did not report HRs | ≤6/12 (BCVA, better eye) | ≥6/12 | NA | OR 2.42 (1.07–5.43) |
| Thigpajaraj et al (2005)* | Categorical analysis and did not report HRs | ≤6/6 to ≤6/9 (PVA, binocular); and ≥6/6 to ≥6/18 (PVA, binocular), and ≥6/18 (PVA, binocular) | ≥6/6 | ≤6/6 to ≤6/9, RR 1.10 (0.01–11.9); and ≥6/6 to ≥6/18, 1.32 (1.22–1.42); and ≥6/18, 1.60 (1.47–1.74) | ≤6/6 to ≤6/9, RR 1.10 (0.01–11.9); and ≥6/6 to ≥6/18, 1.32 (1.22–1.42); and ≥6/18, 1.60 (1.47–1.74) |
| Thompson et al (1989)* | Categorical analysis and did not report HRs | ≤6/7.5 to ≤6/9 (BCVA, better eye); and ≥6/12 to ≥6/18 (BCVA, better eye), and ≥6/24 to ≥6/60 (BCVA, better eye); and ≥6/60 (BCVA, better eye) | ≥6/6 | NA | ≤6/7.5 to ≤6/9, RR 1.62 (0.87–3.01); and ≥6/12 to ≥6/18, 1.81 (0.93–3.53); and ≥6/24 to ≥6/60, 1.72 (0.77–3.84); and ≥6/60, 0.35 (0.08–1.57) |
| Wang et al (2014)* | Effect estimate per unit difference in visual acuity and did not report HRs | (BCVA, worse eye) | NA | OR 1.76 (1.35–2.29) | NA |

The chart used, the eye assessed, follow-up duration, a lower age limit (ie, participants aged <50 years vs those aged ≥50 years), or study design (table 3). However, studies that used best-corrected visual acuity as the vision assessment method reported a significantly higher hazard for mortality (HR 1.45 [95% CI 1.31–1.60]) than those using presenting visual acuity (1.22 [1.13–1.31]; p=0.0055). Using the GRADE framework, we judged the evidence to be of moderate certainty overall, downgrading half a level for risk of bias and half a level for inconsistency. Even though only three of the 28 studies were judged as having a low risk of bias in all domains, meta-regression analyses suggested that the effect estimates were not associated with risk of bias. Measured inconsistency or heterogeneity between studies was not high, but there was some variation in study results. Using this framework, we are moderately confident that the mortality risk associated with vision impairment reported in this study is likely to be close to the true value.38

**Discussion**

This systematic review and meta-analysis summarises the existing evidence on the association between vision impairment and the risk of mortality among adults from 12 countries across five continents. The results support the existence of a consistent association between poor vision and mortality across different study settings, thereby reinforcing the specific importance of vision and eye health to Sustainable Development Goal (SDG) 3, which aims to "ensure healthy lives and promote well-being for all at all ages", as well as to the SDGs more generally.37

This study builds on a previous meta-analysis that considered studies on the association between vision impairment and mortality published before 2015.3 This previous meta-analysis provided evidence that vision impairment could be associated with an increased risk of mortality; however, the study also had several key limitations that we sought to address in the current report. First, the meta-analysis included studies that not...
only assessed vision with objective clinical measures (eg, visual acuity), but also self-reported visual difficulty, and administrative billing codes. Because of the heterogeneous data, the study compared participants with the highest level of vision impairment to those with no vision impairment. This approach could have resulted in misclassification bias, since poor visual acuity, self-reported visual difficulty, and ICD codes could represent distinct constructs. In addition, this approach could have overestimated effect sizes by only including participants in the best and worst vision categories. However, in the meta-regression analyses, the effect size was similar for the 15 studies that assessed vision with visual acuity charts (relative risk 1·36 [95% CI 1·16–1·59]), for the three studies that used ICD codes (1·55 [1·15–2·09]), and for the seven studies that used self-reported visual acuity (1·44 [1·34–1·56]). Another limitation of this previous meta-analysis was not assessing the risk of bias in included studies or not including an overall assessment of the certainty of the evidence.

Figure 4: Risk of bias assessment
Risk of bias was assessed by one of the Quality in Prognostic Studies tool. Green represents low risk of bias, yellow represents a moderate risk of bias, and red represents high risk of bias.

Table 3: Meta-regression analysis results

| Risk of bias | Number of studies | HR (95% CI) | p value |
|--------------|------------------|-------------|---------|
| Low          | 2                | 1·73 (0·85–3·50) | 0·10 |
| Moderate     | 12               | 1·28 (1·18–1·39) | 0·02 |
| High         | 1                | 1·17 (0·63–2·16) | 0·68 |
| Vision chart | 3                | 1·46 (1·29–1·64) | 0·0082 |
| ETDRS chart  | 2                | 1·35 (1·14–1·61) | 0·055 |
| Snellen Tumbling E chart | 2 | 1·28 (1·17–1·40) | 0·027 |

| Vision assessment method | Number of studies | HR (95% CI) | p value |
|--------------------------|------------------|-------------|---------|
| Other or not reported    | 5                | 1·12 (0·95–1·31) | 0·58 |
| Eye                      | 9                | 1·34 (1·19–1·50) | 0·24 |
| Better eye               | 6                | 1·22 (1·12–1·33) | 0·68 |
| Follow-up duration, years | 13              | 1·35 (1·13–1·60) | 0·38 |
| Lower age limit, years   | 7                | 1·35 (1·19–1·54) | 0·10 |
| ≥50                      | 8                | 1·24 (1·15–1·34) | 0·58 |

Estimated HRs for mortality in people with a visual acuity of ≤6/12 versus those with a visual acuity of >6/12, subcategorised by seven variables, with p values from the meta-regression analysis. ETDRS=Early Treatment Diabetic Retinopathy Study. HR=hazard ratio. logMAR=logarithm of minimum angle of resolution.

*Includes Bailey-Lovie charts.
This systematic review and meta-analysis was limited by the wide variation in how studies adjusted for potential confounding variables, which could have biased the findings. Nonetheless, both maximally adjusted and minimally adjusted pooled effect estimates showed a significant association between vision impairment (visual acuity <6/12) and all-cause mortality. Since age is a strong common risk factor for both vision impairment and mortality, studies were only included if they reported, at a minimum, age-adjusted mortality. Studies also adjusted for other important factors that could confound the association between vision impairment and mortality. For example, socioeconomic deprivation, poor access to health care, diabetes, and stroke are a few of the well documented common risk factors for vision impairment and mortality,1 for which models were adjusted in many studies. Some studies, however, might have over-adjusted their statistical models, including for variables that might lie on the causal pathway between vision impairment and mortality. Adjusting for variables hypothesised to be on this causal pathway could bias study results toward the null hypothesis (ie, no effect).

Most included studies were from high-income countries, and additional evidence from regions not represented in the literature would contribute to a more complete understanding of this topic to inform policy. Future studies could also consider adopting standardised measurement and reporting guidelines, as outlined in the main Commission report.4 Furthermore, there is a need for studies to consider the risk of mortality associated with other types of vision impairment that are less commonly assessed, such as contrast sensitivity impairment and peripheral field loss. Mediating pathways between vision impairment and mortality, which could include shared risk factors, such as physical inactivity, social isolation, and disability,10,11 should be investigated. Finally, future calculations of disability-adjusted life-years might include years of life lost due to vision impairment, which could provide a more complete estimate of the overall global burden of vision impairment.

The current study has several key strengths. First, we included multiple additional studies published in 2016–19,19 including those from regions of the world that were not well represented in the previous meta-analysis, such as sub-Saharan Africa (Kenya)1 and east Asia (South Korea).1 Second, we only included studies that assessed visual acuity. Even though this strategy might have resulted in some well designed studies being excluded, it served to strengthen the internal validity of our meta-analysis and to limit misclassification bias. The current investigation also included an assessment of the risk of bias in included studies using the well described QUIPS tool.16 Even though only three included studies were considered to have a low risk of bias across all domains, there was no evidence from the meta-regression analyses that the estimated association was affected by risk of bias. Finally, by use of the GRADE
framework, an overall assessment of the strength of the evidence was described.

The results of this study have important implications for policy and practice. Worldwide, more than 80% of people with vision impairment and blindness live in LMICs, and 55% are women and girls. Four of five cases of vision impairment and blindness are preventable or correctable. In fact, the leading causes of vision impairment and blindness worldwide are cataract and uncorrected refractive error, both of which are readily treatable with inexpensive, cost-effective interventions. Therefore, there is an important opportunity to promote not only health and wellbeing, but also longevity by correcting, rehabilitating, and preventing avoidable vision loss. Policies and strategies for achieving this are outlined in the main Commission report, and have the potential to make important contributions to achieving the SDGs.

Contributors
JREh, JR, BKS, NC, MB, and JREv designed the study. JREh, JR, HB, CNL, JHZ, WW, and JREv collected the data, and DM analysed the data and generated the figures. IG did the literature search. JREh and JREv interpreted the data and drafted the manuscript. JR, DM, HB, CNL, JHZ, WW, BKS, IG, NC, and MB critically revised the manuscript. JREh and JREv accessed and verified all data in the study and JREh, JR, DM, and JREv had full access to all the data in the study. JREh had final responsibility for the decision to submit for publication.

Declaration of interests
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Data sharing
The protocol for this study has been published previously. There are no primary data to be shared.

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