# Global prevalence of visual impairment associated with myopic macular degeneration and temporal trends from 2000 through 2050: systematic review, meta-analysis and modelling. Online supplement.

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Abbreviations/acronyms: MMD = myopic macular degeneration; VI = visual impairment; HE = Health Expenditure

## BACKGROUND WITH ADDITIONAL REFERENCES

Uncorrected refractive error is the main cause of presenting visual impairment (VI) globally, and myopia is the most common refractive error.[1,2] Even with refractive correction, those with high myopia are at risk of a range of associated complications including cataract, glaucoma, retinal pathologies such as tears and detachment, and myopic macular degeneration (MMD).[3-11] MMD alone has been found to cause 12.1% of VI (approximately 200,000 people) in Japan.[12] In other communities with a high prevalence of myopia, MMD has been reported to be the most frequent cause of irreversible blindness.[13,14]

The prevalence of myopia and high myopia has been observed to be increasing globally.[2,3,15,16] Although this trend appears to be most dramatic in younger East Asians,[3,17-20] increasing prevalence of myopia and high myopia has also been observed in the US and Europe.[7,21-23] Thus, current and future trends in lifestyle, education and demographics means global myopia and high myopia prevalence are projected to continue rising worldwide into the foreseeable future.[2] Estimates of the impact of this trend on the epidemiology of VI from MMD would inform planning for prevention and management of the problem. However, despite many prevalence studies on myopia, there are no estimates of the regional or global prevalence of VI caused by high myopia or MMD, or projected changes over future decades.

This paper reviews population-based and blindness registry prevalence studies to estimate the global prevalence of VI and blindness associated with MMD, with modelling and projections through to the year 2050.

## METHODS – ADDITIONAL INFORMATION AND REFERENCING

### Studies, databases and data organization

We searched PubMed (National Library of Medicine) on 9 February 2016 for publications using the following MeSH (Medical Subject Headings) terms: “myopic macular degeneration AND prevalence”, “myopic maculopathy AND prevalence”, and “pathologic myopia AND prevalence”, without any date or language restrictions. Adding terms such as “visual impairment” and/or “blindness” led to a small increase in specificity, but a large reduction in sensitivity, so they were omitted. The search yielded 125, 36 and 56 papers relating to MMD, myopic maculopathy and pathologic myopia, respectively. The abstract of each publication was reviewed and cross-checked by two authors, reducing relevant papers to 68, mainly due to duplication between searches, lack of vision information, and/or lack of epidemiological information. Thirty-nine additional papers were found via key informant advice and reference lists of papers found through PubMed. Review of abstracts reduced this to 3 relevant papers, mainly due to lack of vision information. The full text of each of the 71 remaining papers was reviewed, with inclusion criteria of population-based or blindness-registry studies quantifying prevalence, with sampling representative of whole communities. Exclusions were based on unspecified or ambiguous definitions, failure to specify the number of eligible participants, a participation rate <75%, duplicate data used in other included studies, or inability to differentiate MMD as a cause of VI due to aggregation with other conditions (e.g. age-related macular degeneration).

Country-specific population data for each decade from 2000 through 2050, in 10-year age groups from 0 – 90+ were mostly drawn from the Population Division of the United Nations Department of Economic and Social Affairs.[24] Population data from the International Database of the United States Census Bureau were used for a small number of low population states aggregated within the available United Nations data.[25]

### Meta-analysis and modelling

The variables we analysed against the study time- and place-specific proportion of people with high myopia who have VI or blindness associated with MMD were Human Development Index (HDI), Socio-Demographic Index, mean years of education (male and female separately), elementary school enrolment rate (male and female separately), adult literacy rate (male and female separately), gross domestic product per capita (in price power parity International dollars, and United States dollars, separately), gross national income per capita (in price power parity International dollars, and United States dollars, separately), Gini index, health expenditure per capita (in price power parity International dollars, and United States dollars, separately), health expenditure as a proportion of total gross domestic product, mobile/cellular telephone subscription rates, electric power consumption per capita, and automatic teller machines per capita. All data were taken from the World Development Indicators of the World Bank, except Socio-Demographic Index which was taken from the Institute for Health Metrics and Evaluation.[26,27] The analysis was restricted to >40-year-olds as the evidence suggests that, while VI from MMD can occur in people ≤40 years old, it is strongly concentrated in older age groups.

The equations are based on primary evidence covering 63% of countries and 73% of the global population. We used the equations to calculate the proportion of >40-year-old people with high myopia who have VI and blindness associated with MMD, using each country's health expenditure when that lay within the envelope of the primary evidence (US$62 – US$2835 per capita), or using the closest limit of the envelope for countries with health expenditure outside the envelope.[26] We then combined the country-specific proportions with the >40-year-old prevalence of high myopia for each country, and the meta-analyzed, 0 to 90+ age distribution of VI and blindness associated with MMD.

## RESULTS – ADDITIONAL DETAILS

The 17 studies included in our analysis are summarised in **Table S1**. Six of the 17 studies provided detailed information on the relationship between prevalence of VI/blindness due to high myopia, and age. Verhoeven et al. (2015) found that the cumulative risk of VI from high myopia was negligible until nearly 60 years of age, but then rose significantly faster than in any other refractive state in the Netherlands.[28] While this is not specific to MMD, the differences in causation between high myopia and other refractive states are dominated by MMD.[28] Farber (2003) and Tsai et al. (2008) found a lifelong risk of developing VI from MMD in Israel and Taiwan.[29,30] Xu et al. (2008) found that MMD caused VI and blindness from 40 years of age (the youngest age in their study), but prevalence increased with age in a mixed urban/rural area of China.[31] Two studies found a more constant prevalence of VI and blindness due to MMD across age groups ≥40 years of age in different parts of China.[32,33] Sixteen studies provided location-specific but age-nonspecific data for the prevalence of VI and/or blindness from MMD.[12,13,29-33,34-48]

[Refer to **Table S1** at the end of the text]

In 2000, we estimate the total number of people with VI associated with MMD globally was 4.2 million people, i.e. 0.07% of the world population (95% confidence interval 2.3 million – 9.8 million, 0.04% – 0.16%), that this increased to 7.6 million people, i.e. 0.11% (4.2 – 18.0 million, 0.06 – 0.26%) by 2010, and 10.0 million people, i.e. 0.13% (5.5 – 23.7 million, 0.07 – 0.34%) by 2015. This is projected to increase to 13.1 million in 2020, i.e. 0.17% (7.1 – 30.9 million, 0.09 – 0.40%), 22.2 million in 2030, i.e. 0.26% (11.9 – 51.3 million, 0.15 – 0.58%), 35.7 million in 2040, i.e. 0.39% (18.9 – 80.3 million, 0.22 – 0.82%), and 55.7 million in 2050, i.e. 0.57% (29.0 – 119.7 million, 0.33 – 1.11%).

In 2000, we estimate the total number of people with blindness associated with MMD globally was 1.3 million people, i.e. 0.02% of the world population (95% confidence interval 0.8 million – 3.2 million, 0.01% – 0.05%), that this increased to 2.5 million people, i.e. 0.04% (1.4 – 5.9 million, 0.02 – 0.08%) by 2010, and 3.3 million people, i.e. 0.04% (1.8 – 7.8 million, 0.03 – 0.10%) by 2015. This is projected to increase to 4.3 million in 2020, i.e. 0.05% (2.3 – 10.1 million, 0.03 – 0.13%), 7.3 million in 2030, i.e. 0.09% (3.9 – 16.9 million, 0.05 – 0.19%), 11.8 million in 2040, i.e. 0.13% (6.2 – 26.6 million, 0.07 – 0.27%), and 18.5 million in 2050. i.e. 0.19% (9.6 – 39.7 million, 0.11 – 0.37%).

## ADDITIONAL DISCUSSION

Verhoeven et al. (2015) reports a large-scale study of refractive error specific risks and causes of blindness and low vision.[28] They note that in their population-based sample in the Netherlands with lengthy follow-up time, people with high myopia were at considerably higher risk of permanent VI that started at a younger age, and kept increasing with higher degrees of myopia. They calculated that compared to emmetropes, the risk of VI (World Health Organization criteria for blindness plus moderate and severe VI) was six times higher for those with refractive error between −6.00 D and −10.00 D, and 22 times higher for those with refractive errors of −10.00 D or more. We have controlled for this effect of myopia level by using VI as a proportion of the number of people with high myopia, rather than population prevalence, during our data integration via meta-analysis and modelling across available studies. This mitigates against over- or under-estimating VI associated with MMD based on the wide variation in high myopia prevalence around the world.

Our assumption of a constant proportion of people with high myopia having permanent VI associated with MMD between 2000 and 2050 may be conservative. Verhoeven et al. (2015) and Tideman et al. (2016) show an increasing risk of VI with higher degrees of refractive error even within the high myopia group.[8,28] With projected increases in myopia and high myopia over the decades,[2] the degree of myopia within these groups is also likely to increase, meaning a likely increase in the proportion of people with high myopia experiencing permanent VI associated with MMD. Additionally, even people with low to moderate levels of myopia have an increased risk of developing MMD compared to emmetropes.[3,4] We have not accounted for VI associated with MMD in people with low to moderate myopia, so predicted increases in the number of people with myopia overall, and consequently the increased VI associated with MMD in this group may also contribute to under-estimation by our model. Counteracting these factors leading to the underestimation of VI associated with MMD, successful myopia prevention or control strategies, together with improved detection and treatment of MMD could reduce the number of people progressing to VI. Additionally, if the myopia causation mix changes over time, and if, for example, genetic high myopia and acquired high myopia lead to different rates of VI from MMD, then unforeseen outcomes may eventuate. On balance, and bearing these potential caveats in mind, we feel our model is based on the evidence as it exists today, and is a reasonable balance of these counteracting factors.

Regional differences are evident throughout the projection period, as shown in Table 2. The multiple influences on the model are evident, including prevalence of high myopia, the age groups affected by high myopia, age demographics, and health expenditure. For example, Australasia is modelled to have low rates of VI associated with MMD because it has a relatively low prevalence of high myopia, particularly in older people, and has high health expenditure. Asia Pacific High Income has a relatively high rate of high myopia in older age groups, but a protective influence from high health expenditure. South Asia and South East Asia are modelled to have the highest age-standardized prevalence of VI (0.34% and 0.33% respectively) and blindness (0.12% and 0.11% respectively) from MMD in 2020 and in 2050 (1.32% and 1.08% for VI, and 0.45% and 0.36% for blindness, respectively), because they have lower health expenditure compared to

regions with comparable age demographics and prevalence of high myopia. Sub-Saharan African regions and Oceania are modelled to have relatively low prevalence of VI associated with MMD despite lower health expenditure, because they have relatively lower prevalence of high myopia and relatively younger populations.

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**Table S1.** Summary of findings from the 17 papers included in our analysis, plus six additional papers that provide useful perspective

| | | | | | Calculated all-ages prevalence of WHO-defined VI due to MMD in total population of specified location | | Calculated all-ages prevalence of WHO-defined blindness due to MMD in total population of specified location | |
|---|---|---|---|---|---|---|---|---|
| **Study** | **Location** | **GBD region** | **Sample size** | **Primary data reported** | **Crude** | **Age-adjusted** | **Crude** | **Age-adjusted** |
| Yamada et al. 2010[12] | Mixed urban and rural Japan | Asia-Pacific, high income | 50,367 | Adults aged 40+ from multiple studies across urban and rural Japan, meta-analysed to show MMD causes 12.1% of MSVI and 12.9% of blindness based on BCVA, equating to a prevalence of bilateral VI from MMD in Japan of 0.16% (198,000 people in 2007). (US def) | 0.0673% | 0.0281% | 0.0151% | 0.0061% |
| Nakamura et al. 2010[39] | Rural Japan | Asia-Pacific, high income | 3,594 | Adults in rural Kumejima, Japan, aged 40+: MMD caused 4.8% of MSVI (1 of 21 people) and 1.0% of blindness (1 of 102 eyes) based on BCVA. (WHO def) | 0.0162% | 0.0068% | 0.0081% | 0.0033% |
| Xu et al. 2006[31] | Mixed urban and rural China | East Asia | 4,409 | Adults in urban and rural areas of Beijing, China, aged 40+: MMD caused 32.7% of MSVI (16 of 49 people) and 7.7% of blindness (1 of 13 people) based on BCVA. (WHO def) | 0.1630% | 0.1585% | 0.0425% | 0.0416% |
| Liang et al. 2008[37] | Rural China | East Asia | 6,799 | Adults in rural Handan, China, aged 30+: MMD caused 7.2% of MSVI (8 better-seeing and 17 worse-seeing MSVI eyes of 345 MSVI eyes) and 6.6% of blindness (5 better-seeing and 11 worse-seeing blind eyes out of 243 blind eyes) based on BCVA. (WHO def) | 0.1344% | 0.1307% | 0.0684% | 0.0671% |
| Tang et al. 2015[32] | Urban China | East Asia | 10,234 | Adults in urban Taizhou, China, aged 45+: MMD caused 17.6% of MSVI (91 of 516 people) and 17.2% of blindness (17 of 99 people) based on BCVA. (WHO def) | 0.3999% | 0.3890% | 0.0618% | 0.0606% |
| Yao et al. 2013, combined with Zhao et al. 2010 to clarify definitions/findings[41,49] | Urban China | East Asia | 6,150 | Adults in urban Jiangsu, China, aged 50+: MMD caused 9.4% of MSVI (41 of 437 people) and 10.5% of blindness (31 of 295 people) based on presenting vision. (WHO def) | 0.2689% | 0.2615% | 0.0678% | 0.0665% |
| Wu et al. 2011[42] | Urban China | East Asia | 378 in 2003; 458 in 2006; 514 in 2009 | All-ages blindness registry data in urban Shanghai: blindness prevalence (excluding URE or cataract) estimated to be 0.17%, and 26.1% of blindness (in 2007-2009) was caused by MMD. (WHO def) | Not reported | | 0.0444% | 0.0435% |
| Huang et al. 2009[33] | Urban China | East Asia | 1,399 | Adults in urban Liwan, Guangzhou, China, aged 50+: MMD caused 8.5% of MSVI (12 of 141 people) and 7.9% of blindness (6 of 76 people) based on BCVA. (WHO def) | 0.1763% | 0.1714% | 0.0629% | 0.0616% |
| Tsai et al. 2008[30] | Mixed urban & rural Chinese Taipei | East Asia | 2,912 | All-ages blindness registry data for all of Taiwan: MMD caused 1.4% (2 of 144 cases) of VI in 0-14yo, 7.2% (48 of 668 cases) in 15-49yo, 8.3% (63 of 761 cases) in 50-64yo, and 5.5% (74 of 1339 cases) in 65+yo. (WHO def) | 0.0826% | 0.0637% | 0.0366% | 0.0281% |
| Liu et al. 2001[46] | Urban Chinese Taipei | East Asia | 2,034 | Adults in urban Taipei, Taiwan, aged 50+: MMD caused 25.0% of VI (14 of 56 people) based on BCVA. (WHO def) | 0.1770% | 0.1866% | Not reported | |
| Hsu et al. 2004[44] | Urban Chinese Taipei | East Asia | 1,361 | Adults in urban Shihpai, Taipei, Taiwan, aged 65+: MMD caused 12.5% of bilateral VI (6 of 48 people) based on BCVA. (WHO def) | 0.0647% | 0.0681% | Not reported | |
| Klaver et al. 1998[34] | Urban Netherlands | Western Europe | 6,755 | Adults in urban Rotterdam, Netherlands, aged 55+: MMD caused 5.7% of VI (11 of 192 eyes) and 6.2% of blindness (4 of 64 eyes) based on BCVA. (WHO def) | 0.0318% | 0.0213% | 0.0083% | 0.0055% |

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|---|---|---|---|---|---|---|---|---|
| Farber 2003; Avisar et al. 2006[29,48] | Mixed urban and rural Israel | Western Europe | 18,891 | All-ages blindness registry data in all of Israel: MMD caused 9.5% of newly diagnosed blindness (1,747 people) between 1987 and 1999 based on BCVA; the rate of blindness from MMD rose to a peak of 12% (1,912 people) in 1998 then steadily dropped to 7.4% (1,597 people) by 2003. (WHO def) | Not reported | | 0.0384% | 0.0347% |
| Evans et al. 2004[45] | Mixed urban and rural United Kingdom | Western Europe | 13,900 | Adults from recruited from General Medical Practices across mixed urban and rural areas of the United Kingdom, aged 75+: MMD caused 4.2% of VI (41 of 976 people) based on BCVA. (WHO def) | 0.0429% | 0.0252% | Not reported | |
| Buch et al. 2001[47] | Urban Denmark | Western Europe | 944 | Adults in urban Copenhagen, Denmark, aged 60+: MMD caused 5.6% of MSVI (1 of 18 people) based on BCVA. (WHO def) | 0.0269% | 0.0160% | Not reported | |
| Nowak and Smigielski 2015[40] | Urban Poland | Central Europe | 1,107 | Adults in urban Lodz, Poland, aged 35+: MMD caused 8.3% of bilateral MSVI (1 of 12 people) and 33.3% of bilateral blindness (1 of 3 people) based on BCVA. (US def) | 0.0747% | 0.0480% | 0.0389% | 0.0247% |
| Verhoeven et al. 2015 - data used in analysis of the relative age-dependant risk of VI and blindness associated with MMD[28] | Urban Netherlands | Western Europe | 6,597 | Adults in urban Rotterdam, Netherlands, aged 55+: MMD data from this study was included in Klaver et al. 1998; Verhoeven et al. 2015 provides data on the age spread of myopia-related vision loss that is used in our meta-analysis of age-specific risk of VI from MMD. (WHO def) | N/A | | N/A | |
| **Sources that provided perspective, but were excluded from the main analysis for reasons noted on each study:** | | | | | | | | |
| Iwase et al. 2006 - excluded as a stand-alone paper as was included in Yamada et al. 2010 meta-analysis[13] | Urban Japan | Asia-Pacific, high income | 2,977 | Adults in urban Tajimi, Japan, aged 40+: MMD caused 9.2% of MSVI (7 of 76 eyes) and 22.4% of blindness (11 of 49 eyes) based on BCVA. (WHO def) | 0.1764% | 0.0736% | 0.1073% | 0.0434% |
| Zheng et al. 2011 - excluded as selected Indian Singaporeans only, and can't be considered nationally representative[43] | Urban Singapore | Asia-Pacific, high income | 3,400 | Indian adults in urban Singapore aged 40+: MMD caused 6.2% of bilateral MSVI (9 of 145 people) and 2.9% of blindness (2 of 70 eyes) based on BCVA. (US def) | 0.0959% | 0.0812% | 0.0110% | 0.0094% |
| Van Newkirk 1997 - excluded due to ambiguity of what is aggregated within "myopic degenerations"[38] | Urban Hong Kong SAR | East Asia | 355 | Adults in urban Hong Kong, China, aged 40+: MMD caused 31.2% of bilateral moderate VI (5 of 16 people) based on BCVA. (WHO def) | 0.6529% | 0.5435% | Not reported | |
| Cedrone et al 2006 - excluded due to ambiguity of what is aggregated within "myopia"[35] | Rural Italy | Western Europe | 843 | Rural adults on Ponza island, Italy, aged 40+: "Myopia" caused 4.5% of MSVI (3 of 67 eyes) and 13.9% of blindness (5 of 36 eyes) based on BCVA. (WHO def) | 0.2720% | 0.1248% | 0.1699% | 0.0779% |
| Cotter et al. 2006 - excluded because selected Latino Americans only, and can't be considered nationally representative[36] | Urban United States of America | Targeted sample within North America High Income | 6,344 | Select population of Latino adults in urban Los Angeles, USA, aged 40+: MMD caused 1.8% of MSVI (1 of 55 people) and 16.7% of blindness (2 of 12 people) based on BCVA. (WHO def) | 0.0176% | 0.0196% | 0.0116% | 0.0129% |
| Vongphanit et al. 2002 – excluded because although an overall VI rate is provided, there is no direct way to determine the prevalence of VI or blindness | Regional Australia | Representative sample within Australasia | 3,654 | Eligible residents aged 49+ who attended the Blue Mountains Eye Study: myopic retinopathy (including staphyloma, lacquer cracks, Fuch's spot and myopic chorioretinal atrophy) was found in 67 eyes from 44 participants (a prevalence of 1.4% in women and 1.0% in men). Prevalence increased from 1% in eyes with myopia <3D to over 50% in eyes with myopia ≥9D. VI (US def) was present in 39% of affected eyes overall, but no details | 0.1115% (with assumptions made by us re information not specified in the paper) | 0.0811% (with assumptions made by us re information not specified in the paper) | Not reported | |

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| associated with MMD based on the data published[50] | | | | were published regarding the distribution of this VI between eyes vs people, age groups, or type of myopic retinopathy. Assumptions were needed to calculate VI from MMD. | | | |

*Farber et al. 2003 and Avisar et al. 2006 reviewed the same blindness registry data in Israel - different aspects of the data was taken from each paper.

MMD = Myopic Macular Degeneration; MSVI = Moderate and Severe Visual Impairment; VI = Visual Impairment (MSVI + blindness); BCVA = Best Corrected Visual Acuity; URE = Uncorrected Refractive Error; WHO = World Health Organization