Association of Sex with the Global Burden of Age-related Macular Degeneration

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Abstract

Background: Age-related macular degeneration (AMD) is the third leading cause of blindness and affects approximately 196 million people. This study aims to explore the association of sex with the global burden of AMD by year, age, and socioeconomic status using disability-adjusted life-years (DALYs).

Methods: Global, national sex-specific DALY numbers, crude DALY rates, and age-standardized DALY rates caused by AMD, by year and age, were extracted from the Global Burden of Disease Study 2017. The human development index (HDI) in 2017 was extracted as an indicator of national socioeconomic status from the Human Development Report 2018 (HDR 2018). Pearson correlation and linear regression analyses were conducted to investigate the association between socioeconomic status and sex inequality of AMD.

Results: Differences in the sex-specific global burden of AMD have persisted since 1990 to 2017. Female individuals had higher burden than male individuals of the same age in 2017, and the differences gradually increased after 55 years and maximized at 80 years or older with 105.41 DALYs rates in female vs 81.00 DALYs rates in male. The paired Wilcoxon signed rank test indicated that female had higher age-standardized DALY rates than male had ($Z = -6.520$, $P < 0.001$) and countries with lower HDI values had higher age-standardized DALY rates among both sexes. DALY rate ratio and sex differences in age-standardized DALY rates were positively associated with HDI in both Pearson correlation analyses and linear regression analyses of AMD. ($P < 0.05$).

Conclusions: Although global blindness and vision impairment health care is progressing, sex inequality in AMD burden remained persistent since the past few decades. These findings might raise more public attention to the gender differences in global AMD burden and the association between the sex-related global burden and socioeconomic status.

Background

Worldwide, age-related macular degeneration (AMD) is the third leading cause of blindness and affects approximately 196 million people[1, 2], particularly older women[3]. AMD causes substantial societal economic problems, and the annual direct medical cost for AMD in the United States was \$575 million in 2004 and is estimated to increase to \$845 million in 2020[4]. With increased life expectancies, the prevalence of blindness caused by AMD is increasing, which markedly diminishes the quality of life[5]. Previous studies have shown that blindness increases the risk of motor vehicle collisions[6] and cognitive impairments[7], especially in women aged 69 or older with osteoporotic fractures[8], and reduces physical activity[9]. Inequality in socioeconomic factors (such as education, religiosity, socioeconomic status and labor productivity) may make it more difficult for women to seek timely eye care treatment[10, 11], and women are more likely to have blindness compared to men[12, 13]. According to the Global Burden of Disease (GBD) Study 2017[14], the prevalence of blindness was 17.86% among women vs 14.52% among men. A meta-analysis revealed that women accounted for almost two-thirds of the world's blind

people[13], and research from three major population-based studies identified gender inequities in the form of an increased risk for AMD among women[15]. Blindness and severe visual impairment caused by AMD could be reduced if women received the same eye care as men[16]. Reducing the sex difference in the prevalence of AMD might effectively reduce blindness, which would be progress in global health care for eyes.

In the GBD study, disability-adjusted life year (DALY) is a new metric for measuring global health burden by integrating mortality with morbidity and disability information into a single unit. Ono et al.[17] first used DALY data from the GBD study in 2004 to explore the global inequality in cataracts, glaucoma, retinal detachment (RD) and macular degeneration (MD), and they found that females had a greater burden of RD than males. GBD studies over the last few years have demonstrated that the health burden of AMD is unequal worldwide. The global burden of blindness is not equal across genders, but this inequality has not yet been investigated. More attention should be given to gender inequality in AMD to increase awareness and to design better healthcare policies with respect to vision rehabilitation.

Thus, the purpose of this study was to explore the sex differences in the global burden of AMD by year, age and socioeconomic status using DALY data from the most recent GBD Study, which was conducted in 2017[14].

Methods

Study Design

This is an international, comparative burden-of-disease study. This study does not require ethics approval and informed consent, as GBD study data and the HDR 2018 can be downloaded directly from the Open Access Database.

Sex-specific Global Burden

According to the International Statistical Classification of Diseases and Related Health Problems (10th revision), codes H35.3-H35.389 are mapped to AMD in the GBD Study 2017[18]. Methods to calculate the DALYs were described in the GBD Study 2017[14]. Since the GBD Study 2017 contains the most recently collected data, the following DALYs data caused by AMD were extracted from the Global Health Data Exchange[19]: (1) global sex-specific DALY numbers, crude DALY rates (per 100,000 population), and age-standardized DALY rates (per 100,000 population) in 1990, 1995, 2000, 2005, 2010, 2015 and 2017; (2) global sex- and age-specific DALY numbers and crude DALY rates in 2017; and (3) national sex-specific age-standardized DALY rates in 2017.

National Socioeconomic Status

Human development index (HDI), as an indicator of national socioeconomic status, is a composite index measures health, education and income. The HDI ranges from 0 to 1 (details on how the HDI is calculated are available at http://hdr.undp.org/sites/default/files/hdr2016_technical_notes.pdf), with a higher value indicating a higher socioeconomic status. Countries were classified into four groups by HDI values in 2017[20]: low human development ($0 < \text{HDI} < 0.550$), medium human development ($0.550 \leq \text{HDI} < 0.700$), high human development ($0.700 \leq \text{HDI} < 0.800$), and very high human development ($0.800 \leq \text{HDI} < 1$). The national HDI in 2017 were extracted from the Human Development Report (HDR) 2018[20] released by the United Nations Development Programme (UNDP).

Statistical Analysis

The Wilcoxon signed rank test[21, 22] was conducted to compare global sex differences in age-standardized DALY rates caused by AMD and to further assess sex differences in each country group based on the HDI. Pearson correlation analyses and linear regression analyses were performed to explore the relationships of sex-specific global burden of AMD in age-standardized DALY rates, female to male age-standardized DALY rate ratios and sex difference age-standardized DALY rate with HDI. SPSS 23 (IBM, Chicago, Illinois, USA) was used for all statistical analyses, with $P < 0.05$ being considered statistically significant.

Results

Global Burden of AMD by Sex

Differences in the sex-specific global burden of AMD persisted from 1990 to 2017, as seen in Fig 1A, the total DALY numbers among females (151,958.38 in 1990 vs 307,576.72 in 2017) and males with AMD (102,999.44 in 1990 vs 223,157.46 in 2017) grew rapidly, and the sex difference slowly increased in recent decades. After controlling for population size during the same period, sex differences in crude DALY rates (DALYs per 100,000 population) also persisted between 1990 and 2017 (Fig 1B), while the differences were reduced. The crude DALY rates of female vs male were 5.68 vs 3.79 in 1990 and 8.08 vs 5.82 in 2017. After controlling for both population size and age structure, the sex-specific global burden of AMD in age-standardized DALY rates varied consistently over the past several decades. As shown in Fig 1C, the sex difference changed irregularly from 1990 (7.28 in females and 6.13 in males) to 2005 (7.51 in females and 6.32 in males) and reached a peak in 1995 (7.62 in females and 6.37 in males). Since 2005, the sex difference has been decreasing continuously, the DALYs rates of females and males were approximately 7.16 and 6.26, respectively in 2017.

Global Sex-Specific Burden of AMD by Age

Estimates of the sex-specific global DALY burden of AMD for persons older than 45 years were available from the GBD Study 2017. As shown in Fig 2, females had a higher burden than males of the same age in

2017. In general, DALY numbers of AMD decreased briefly after age 65 and then increased again after age 75 (Fig 2A). After controlling for population size, crude DALY rates increased with age. Sex differences in crude DALY rates were almost nonexistent between the ages of 45 to 55 years old, and the differences gradually increased after the age of 55 and peaked at the age of 80, with 105.41 DALYs per 10,000 in female vs 81.00 DALYs per 10,000 in male.

Sex-Specific Burden of AMD by National Socioeconomic Status

According to the data provided by the HDR 2018[20], which include 189 countries' HDI values, we extracted the corresponding 2017 national age-standardized DALY rates of the 189 countries. Unfortunately, DALY data from Hong Kong, Liechtenstein, Palau, Eswatini, Saint Kitts and Nevis could not be obtained until the end of our research. Ultimately, national age-standardized DALY rates and the corresponding HDI values of 184 countries were used to study the sex difference global burden of AMD by socioeconomic development. The paired Wilcoxon signed rank test indicated that females had higher age-standardized DALY rates than males ($Z = -6.520$, $P < 0.001$). HDI values in 2017 of 184 countries were extracted from the HDR 2018[20], including 57 countries with very high HDI values, 51 countries with high HDI values, 38 countries with medium HDI values, and 38 countries with low HDI values.

As shown in Fig 3, females had significantly higher age-standardized DALY rates for AMD than males across all HDI categories. Generally, countries with lower HDI values had higher age-standardized DALY rates among both sexes. Linear regression analysis indicated that the HDI had a significant effect on the age-standardized DALY rate in both genders (female: $r = -0.137$, $P > 0.05$; male: $r = -0.222$, $P < 0.05$). The DALY rate ratio (female to male) in age-standardized DALY rates was positively associated with the HDI in both Pearson correlation analyses ($r = 0.207$, $P < 0.05$) and linear regression analyses (standardized $\beta = 0.207$, $P < 0.05$). Further analyses revealed that sex differences (female minus male) in age-standardized DALY rates were positively associated with the HDI in both Pearson correlation analyses ($r = 0.172$, $P < 0.05$) and linear regression analyses of AMD (standardized $\beta = 0.172$, $P < 0.05$) (Fig 4).

Discussion

This study revealed that sex inequalities in the global burden of AMD have persisted since 1990 and have barely improved over the past few decades. The AMD burden in age-standardized DALY rates showed irregularity from 1990 to 2000 and then showed a small decline after 2000. Generally, females had a higher burden of AMD than males at all ages after 55 years old, and gender inequality in AMD burden increased with age. Socioeconomic status may be an important factor that affects the global AMD burden.

Abou-Gareeb et al[13] conducted a meta-analysis of published, population-based surveys to explore the sex difference of blindness and found that women accounted for 64.5% of all blind people, which

equaled approximately two-thirds of the burden of global blindness. They also found that blindness in women was more common among elderly individuals. Moreover, several studies have indicated that women might be more sensitive to diseases that cause blindness, and men are twice as likely as women to be able to access eye care in all regions of the world[16, 23, 24]. Social, cultural, biological and economic differences between females and males are more likely to expose women to a higher global AMD burden[25, 26], such as lower diagnostic and therapeutic efforts for women[27, 28] and longer life expectancies for women[29]. A lack of financial decision-making authority within the family and lower incomes may inhibit women from being able to pay for eye care services[30, 31]. In addition, women's child care responsibilities may make it difficult for them to leave home to access more eye care. All of these studies are similar to our findings, there are considerable sex differences in global AMD burden, such that women have a larger burden of AMD.

This study revealed that the global health burden of AMD increased with age but was almost invariable by year. However, in contrast to our results, Ramke et al[32] conducted a review that showed a decrease in the prevalence of blindness in both sexes in all regions of the world from 1990 to 2010. They also found that women had a higher prevalence of blindness than men in all regions of the world. Increasing age was consistently and strongly associated with AMD[3, 33, 34], and a systematic review and meta-analysis of studies conducted in Asian populations identified age as an independent risk factor for AMD[35]. These findings were in line with our study, as age is the most important demographic factor associated with AMD. Our research also notes that there were significant gender differences in the global AMD burden in most regions. Women had a significantly higher burden than men across all HDI categories. A population-based study by the Blue Mountains Eye study showed that the prevalence of wet AMD among females was two times higher than that among males[36]. However, some studies have shown that female sex was considered a weak risk factor and was not closely related to AMD[33, 34]. In a meta-analysis by Wong et al, there was no evidence of gender differences in the prevalence of early-onset or late-onset AMD[1]. It seems that no final conclusion has yet been reached on the presence of gender differences in AMD. The population-based cross-sectional study by Singapore Eye Study revealed that early-onset AMD was more common in Chinese and Indian people than in Malay people[37]. Two other previous studies suggested that the prevalence of AMD was similar between Asian and white populations[38, 39]. However, the Beijing Eye Study showed that visual impairment due to AMD was comparatively uncommon in rural and urban regions of China, and such impairments were markedly less common in these regions than in Western countries[40]. In summary, the global AMD burden differed considerably across regions. Our study found that in low-HDI areas, people had a higher global AMD health burden, and females had a higher burden than males. A study conducted in Chicago was consistent with our findings, suggesting that more women had converted to neovascular AMD than men[41], resulting in a higher global AMD burden. However, in our results, the global AMD burden of very-high-HDI countries did not show the same regularities (Fig. 3). We thought that this finding might be related to economic growth, which leads to improvements in the social medical care system, an increased awareness of eye services, and increases in life expectancy, thereby resulting in a higher AMD health burden. Last, we found that the global blindness and vision impairment burden among both males and

females was positively related to the HDIs of countries. These inconsistent findings might be attributed to differences in the study countries and sample sizes. According to the GBD Study, we used the most reliable and up-to-date epidemiological data, which revealed the presence of sex-specific differences in the global AMD burden.

As in the 2017 GBD study, the limitations of statistical assumptions and data sources could not be completely avoided despite continued methodological advances and data enrichments[14, 18]. The GBD study might also be biased by the geographic variations in DALY estimates because of the use of aggregate data at the national level instead of district data, the low response rates, or other factors. Thus, the conclusions drawn herein might not be applicable to a specific district, although the GBD study provided an estimation of sex differences in the global health burden of AMD. Second, the population-based GBD studies that reported on DALYs due to blindness and vision impairment did not include the diagnostic subtypes of these impairments, such as wet AMD vs dry AMD. Finally, due to our limited access to the latest data extracted from the GBD study, the most recent DALY data are always lagging. Thus, in 2020, we can only conduct an analysis of the global sex inequality in the health burdens from 2017. Nevertheless, GBD studies are updated annually, and further exploration of long-term and richer data on sex differences in global blindness and vision impairment burden will be conducted.

In conclusion, this study revealed that the global burden of sex difference in AMD has persisted for decades, and little improvement has been achieved. The global health burden of AMD among both sexes tends to increase with age. In addition, females have a higher health burden than males in AMD in all regions around the world, especially among females in low-HDI countries and elderly females. The findings of this study might increase awareness of the gender differences in global AMD burden and the association between sex-related global burden and socioeconomic status.

Conclusions

This study first reveals the current sex differences in the global burden and health inequality of AMD, which will be helpful to make better health policies tailored for the global public, and helpful to AMD rehabilitation.

Abbreviations

AMD: Age-related macular degeneration; DALYs: Disability-adjusted life-years; HDI: Human development index; HDR: Human Development Report; GBD: Global Burden of Disease; RD: Retinal detachment; UNDP: United Nations Development Programme

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during and/or analysed during the current study are available in the Global Health Data Exchange repository, <http://ghdx.healthdata.org/gbd-results-tool> and United Nations Development Programme repository, <http://hdr.undp.org/>.

Competing interests

The authors declare that they have no competing interests.

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Not applicable

Authors' contributions

XCST contributes to study design and drafting of the manuscript. JW contributes to study design, data analysis and writing of the manuscript. JYZ and XNY contribute to data analysis and manuscript drafting. XJT contribute to study design. All authors read and approved the final manuscript.

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Figures

Figure 1

Global Sex-Specific Burden of Age-related Macular Degeneration from 1990 to 2017. (DALY numbers are given in thousands).

Figure 1

Global Sex-Specific Burden of Age-related Macular Degeneration from 1990 to 2017. (DALY numbers are given in thousands).

Figure 2

Global Sex-Specific Age-related Macular Degeneration Burden by Age in 2017.

A. All DALYs

B. Crude DALYs rate

Figure 2

Global Sex-Specific Age-related Macular Degeneration Burden by Age in 2017.

Figure 3

Sex Difference in Age-Standardized Disability-Adjusted Life-year (DALY) Rates by the HDI Category (paired Wilcoxon signed rank test: *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$).

Figure 3

Sex Difference in Age-Standardized Disability-Adjusted Life-year (DALY) Rates by the HDI Category (paired Wilcoxon signed rank test: *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$).

Figure 4

Female and Male Age-Standardized Disability-Adjusted Life-year (DALY) Rates of Age-related Macular Degeneration.

Figure 4

Female and Male Age-Standardized Disability-Adjusted Life-year (DALY) Rates of Age-related Macular Degeneration.