The decreasing prevalence of non-refractive visual impairment in older Europeans: a meta-analysis of published and unpublished data

Cécile Delcourt[1], PhD, Mélanie Le Goff[1], MSc, Therese von Hanno[2,3], MD, Alireza Mirshahi[4,5], MD, Anthony P Khawaja[6], MD, Virginie J.M. Verhoeven [7,8], MD, Ruth E Hogg[9], PhD, Eleftherios Anastosopoulos[10], PhD, Maria Luz Cachulo[11,12], MD, René Höhn[5,13], MD, Christian Wolfram[5], MD, Alain Bron[14], MD, Stefania Miotto[15], MD, Isabelle Carrière[16,17], PhD, Johanna M Colijn[7,8], MD, Gabriëlle HS Buitendijk [7,8], MD, Jennifer Evans[18], PhD, Dorothea Nitsch[18], MD, Panayiota Founti[10], MD, Jennifer LY Yip[6,18], PhD, Norbert Pfeiffer[5], MD, Catherine Creuzot-Garcher[14], MD, Rufino Silva[11,12,19], MD, Stefano Piermarocchi[20], MD, Fotis Topouzis[10], MD, Geir Bertelsen[3,21], MD, Paul J Foster[22,23], MD, Astrid Fletcher[18], MD, Caroline CW Klaver[7,8], MD, Jean-François Korobelnik[1,24], MD, for the European Eye Epidemiology (E3) consortium*

*E3 consortium are listed as online-only material (available at aaojournal.org).

1 Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team LEHA, UMR 1219, F-33000 Bordeaux, France

2 UiT The Arctic University of Norway, Tromsø, Norway.

3 Nordland Hospital, Bodø, Norway

4 Dardenne Eye Clinic, Bonn-Bad Godesberg, Bonn, Germany

5 Department of Ophthalmology, University Medical Center Mainz, Mainz, Germany

6 Department of Public Health & Primary Care, University of Cambridge, Cambridge, United Kingdom

7 Department of Ophthalmology, Erasmus Medical Center, Rotterdam, the Netherlands

8 Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands

9 Centre for Experimental Medicine, Queen's University Belfast, Grosvenor Road, Belfast, Northern Ireland

10 Department of Ophthalmology, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece

11 Department of Ophthalmology, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal

12 Association for Innovation and Biomedical Research on Light and Image (AIBILI), Coimbra, Portugal.

13 Department of Ophthalmology, Inselspital, University Hospital Bern, University of Bern, Bern, Switzerland

14 Department of Ophthalmology, University Hospital, Eye and Nutrition Research Group, Dijon, France

15 Department of Ophthalmology, Camposampiero Hospital, Camposiero, Italy

16 Inserm, U1061, Montpellier, F-34093 France

17 Univ Montpellier, Montpellier, F-34000 France

18 London School of Hygiene & Tropical Medicine, London, United Kingdom

19 Faculty of Medicine, Institute for Biomedical Imaging and Life Sciences (IBILI), University of Coimbra, Coimbra, Portugal

20 Department of Ophthalmology, University of Padua, Padua, Italy

21 University Hospital of North Norway, Tromsø, Norway

22 Integrative Epidemiology, UCL Institute of Ophthalmology, London EC1V 9EL, United Kingdom

23 NIHR Biomedical Research Centre at Moorfields Eye Hospital, London, United Kingdom

24 CHU de Bordeaux, Service d'Ophtalmologie, Bordeaux, F-33000, France

Corresponding author/reprints: Cécile Delcourt, Inserm U1219, Université de Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux Cedex. Tél: +33 5 57 57 11 91; email: cecile.delcourt@u-bordeaux.fr

Meeting presentation: Presented at the annual ARVO (Association for Research in Vision and Ophthalmology) meeting in May 2014 (Delcourt C, European Eye Epidemiology (E3) consortium. Prevalence of visual impairment in elderly Europeans: geographical and temporal trends. *Invest Ophthalmol Vis Sci. ARVO Meeting Abstracts* 2014 55:6081).

Financial support:

ALIENOR The Alienor study received financial support from Laboratoires Théa (Clermont-Ferrand, France). Laboratoires Théa participated in the design of the study, but no sponsor participated in the collection, management, statistical analysis and interpretation of the data, nor in the preparation, review or approval of the present manuscript.

Coimbra Eye Study The Coimbra Eye Study received financial support exclusively from Novartis. Novartis did not participate in the study design or the collection, management, statistical analysis, interpretation or publication of the study results.

EPIC-Norfolk EPIC-Norfolk infrastructure and core functions are supported by grants from the Medical Research Council (G1000143) and Cancer Research UK (C864/A14136). The clinic for the third health examination was funded by Research into Ageing (262). Yip is a National Institute for Health Research (NIHR) Clinical Lecturer. Mr Khawaja is a Wellcome Trust funded Clinical Research Fellow. Prof Foster has received additional support from the Richard Desmond Charitable Trust (via Fight for Sight). Prof Foster and Peto received funding from the Department for Health through the award made by the National Institute for Health Research to Moorfields Eye Hospital and the UCL Institute of Ophthalmology for a specialist Biomedical Research Centre for Ophthalmology. None of the funding organisations had a role in the design or conduct of the research.

EUREYE The EUREYE Study was supported by grant QLK6-CT-1999-02094 from the European Commission Vth Framework. Additional funding for cameras was provided by the Macular Disease Society. The Alicante site was supported by grants FIS 01/1692E and RCESPC03/09 from the Spanish

Ministry of Health; by Centro de Investigacion Biome´dica en Red de Epidemiologia´ y Salud Pu´ blica; and by grants CTGCA/2002/06 and G03/136 from the Generalitat Valenciana. None of the funding organizations had a role in the design or conduct of the research.

Gutenberg Health Study The Gutenberg Health Study is funded through the government of Rhineland-Palatinate („Stiftung Rheinland-Pfalz für Innovation“, contract AZ 961-386261/733), the research programs “Wissen schafft Zukunft” and “Center for Translational Vascular Biology (CTVB)” of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim, PHILIPS Medical Systems and Novartis Pharma, including an unrestricted grant for the Gutenberg Health Study. Funders were involved in the development of the study design as scientific consultants. However, they played no role in data collection, analysis, decision to publish, or preparation of the manuscript.

Montrachet This study was funded by public institutions; the Regional Council of Burgundy and an interregional grant from the Ministry of Health (PHRC Interregional).

MRC Trial The MRC trial of assessment of older people was funded by the UK Medical Research Council, the Department of Health for England & Wales and the Scottish Office. The funding organizations had no role in data collection, data analysis, data interpretation, or writing of this research

PAMDI The PAMDI Study project was designed by the Department of Ophthalmology of the University of Padua and the National Italian Institute for Research on Food and Nutrition, Rome, Italy. The municipalities of Padua, Teolo and Torreglia supported patients’ recruitment for the urban and rural sample, respectively. Data collection was performed by the Department of Opthalmology of the University of Padua and by the Eye Clinic of Abano Terme Hospital, Abano Terme, Italy, and Ibis informatica s.r.l., Milan, Italy. The study was conducted in collaboration with the Reading Centre of the Moorfields Eye Hospital NHS Foundation Trust, London, UK. No sponsor was involved in statistical analysis and manuscript preparation.

POLA This study was supported by the Institut National de la Santé et de la Recherche Médicale (Inserm), Paris, France; by grants from the Fondation de France, Department of Epidemiology of Ageing, Paris, the Fondation pour la Recherche Médicale, Paris, the Région Languedoc-Roussillon, Montpellier, France and the Association Retina-France, Toulouse; and by financial support from Rhônes Poulenc, Essilor, Specia and Horiba ABX Montpellier, and the Centre de Recherche et d'Information Nutritionnelle, Paris. The sponsors and funding organizations played no role in the design or conduct of this research.

Rotterdam Study The Rotterdam Study was supported by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), the Municipality of Rotterdam, UitZicht, Stichting Combined Ophthalmic Research Rotterdam (CORR), , the Netherlands Genomics Initiative/NWO, Center for Medical Systems Biology of NGI, Lijf en Leven, M.D. Fonds, Henkes Stichting, Stichting Nederlands Oogheelkundig Onderzoek, Swart van Essen, Bevordering van Volkskracht, Blindenhulp, Landelijke Stichting voor Blinden en Slechtzienden, Rotterdamse Vereniging voor Blindenbelangen, OOG, Algemene Nederlandse Vereniging ter

Voorkoming van Blindheid, the Rotterdam Eye Hospital Research Foundation, Erasmus Trustfonds, and Topcon Europe. The authors are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists.

Thessalonki Eye Study The Thessaloniki Eye Study was supported in part by: International Glaucoma Association, London, UK; UCLA Center for Eye Epidemiology, Los Angeles, CA; Health Future Foundation, Creighton University, Omaha, NE; Texas Tech University Health Sciences Center, Lubbock, TX; Pfizer, Inc., New York, NY; Glaucoma Research Education Foundation, Indianapolis, IN; Pharmacia Hellas, Athens, Greece; Novartis Hellas, Athens, Greece. All the grants were unrestricted.

Tromsø Eye Study received funding from the Norwegian Extra Foundation for Health and Rehabilitation through EXTRA funds, the Research Council of Norway, the Northern Norway Regional Health Authority and the University of Tromsø.

Conflict of interest:

CD is consultant for Allergan, Bausch+Lomb, Laboratoires Théa, Novartis, and Roche, and has received grants from Laboratoires Théa, all outside the submitted work. RS is member of Advisory Board for Allergan, Alimera, Bayer, Alcon, Novartis, and THEA, outside the submitted work. AK is consultant for Novartis and Allergan, outside the present work. All other authors declare no competing interests .

Running head:

Prevalence of visual impairment in Europe

ABBREVIATIONS:

AMD: age-related macular degeneration

BCVA: best-corrected visual acuity

E3: European Eye Epidemiology consortium

GBD: Global Burden of Diseases, Injuries and Risk Factors

PVA: presenting visual acuity

VEGF: vascular endothelial growth factor

WHO: World Health Organization

ABSTRACT

Topic: Our objective was to estimate the prevalence of non-refractive visual impairment and blindness in European subjects aged 55 years and older.

Clinical relevance: Few visual impairment and blindness prevalence estimates are available for the European population. In addition, many of the data collected in European population-based studies are currently unpublished and have not been included in previous estimates.

Methods: Fourteen European population-based studies participating in the European Eye Epidemiology (E3) consortium (N=70,723) were included. Each study provided non-refractive visual impairment and blindness prevalence estimates stratified by age (10 years strata) and gender. Non-refractive visual impairment and blindness were defined as best-corrected visual acuity (BCVA) worse than 20/60 and 20/400 in the better eye, respectively. Using random effects meta-analysis, prevalence rates were estimated according to age, gender, geographical area and time period (1991-2006; 2007-2012). Since no data were available for Central and Eastern Europe, population projections for numbers of affected people were estimated using Eurostat population estimates for European high-income countries in 2000 and 2010.

Results: The age-standardized prevalence of non-refractive visual impairment in people aged 55 years or older decreased from 2.22% (95% confidence interval (CI): 1.34-3.10) in 1991-2006, to 0.83% (95% CI: 0.38-1.28) in 2007-2012. It strongly increased with age in both time periods (up to 15.69 % and 4.39% in subjects aged 85 or more in 1991-2006 and 2007-2012, respectively). Age-standardized prevalence of visual impairment tended to be higher in women than men in 1991-2006 (2.67% versus 1.88%), but not in 2007-2012 (0.87% versus 0.88%). No differences were observed between Northern, Western and Southern regions of Europe. The projected numbers of affected older inhabitants in European high-income countries decreased from 2.5 million affected subjects in 2000 to 1.2 million in 2010. Of those, 584,000 were blind in 2000, by comparison with 170,000 in 2010.

Conclusions: Despite the increase in the European older population, our study indicates that the number of visually impaired people has decreased in European high-income countries in the last twenty years. This may be due to major improvements in eye care and prevention and/or decreasing prevalence of eye diseases.

Visual impairment and blindness have profound human and socioeconomic consequences in all societies. People with vision loss experience a reduced quality of life,[1, 2] greater difficulty with daily living and social dependence,[3, 4] higher rates of depression [5, 6] and an increased risk of falls and related hip fractures.[7, 8] Worldwide, vision loss is a leading cause of disability. [9] The costs of lost productivity, rehabilitation, and education of the blind constitute a considerable economic burden for the individuals, their family, and society. Vision loss also incurs both direct health care costs and indirect costs of lost productivity, welfare, and informal care[10]. The global annual cost of visual impairment was estimated to be 3000 billion US dollars (563 billion US dollars for Europe).[11] Since 1999, prevention of visual impairment and blindness has been a priority of the World Health Organization (WHO), through its joint program with the International Agency for the Prevention of Blindness, known as "VISION2020 –the Right to Sight".[12] In 2013, the World Health Assembly adopted a new global action plan for the prevention of avoidable blindness and visual impairment for the period 2014–2019.[13]

A common cause of visual impairment is refractive error (such as myopia, hyperopia, astigmatism or presbyopia), which can be corrected using optical correction (spectacles or contact lenses).[14] Thus, visual impairment due to refractive error is often termed "correctable visual impairment", while visual impairment from other causes is often termed "uncorrectable visual impairment" or "non-refractive visual impairment". Worldwide, major causes of non-refractive visual impairment currently are age-related eye diseases (cataract, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy).[15] For this reason, visual impairment is much more frequent in older individuals. Globally, 65% of visually impaired and 82% of the blind subject are aged 50 years or more.[15]

While estimates of the prevalence of visual impairment and blindness are regularly published for the USA,[16-19] such estimates are less reported for the European population. Although many epidemiological studies have been conducted in Europe,[2, 20-24] there have been few attempts to harmonize these studies in order to provide estimations of the prevalence of visual impairment throughout the continent. In 2011, the EUREYE study suggested that the prevalence of visual impairment and blindness may be higher in Southern Europe than in Northern Europe (with the exception of Tallinn, Estonia, demonstrating prevalence rates as high as in Southern Europe) and that European women may be more affected than European men.[2] However, this study was performed in 6

cities from 6 European countries (Bergen, Norway; Tallinn, Estonia; Belfast, UK; Paris-Créteil, France; Verona, Italy; Thessaloniki, Greece), with a total of 4166 participants, and may not be representative of the whole European continent. In 2014, prevalence rates for the European continent were estimated in a systematic review and meta-analysis performed by the expert group convened for the Global Burden of Diseases, Injuries and Risk Factors (GBD).[25, 26] This meta-analysis suggests that the prevalence of visual impairment and blindness has decreased in recent decades in all continents, and in particular in Europe. It also showed higher prevalence rates of visual impairment in Central and Eastern Europe compared with Western Europe, and somewhat higher prevalence of visual impairment in women compared with men. However, because this meta-analysis relied on published data, the definitions (thresholds, type of optical correction) and reporting (in particular age groups) of visual impairment differed widely among the included studies, although these differences were in part addressed by the authors using complex statistical modeling. In addition, many European population-based studies have collected data on visual impairment without publishing prevalence estimates, and thus could not be included in this meta-analysis.

The European Eye Epidemiology (E^3) consortium is a collaborative initiative between 41 epidemiological studies across Europe to share and meta-analyze epidemiological data on ocular health.[27] The aim of the present study was to provide more precise estimates of the prevalence of non-refractive visual impairment in older Europeans and to assess potential temporal trends and geographical variations.

POPULATIONS AND METHODS

Studies and participants

To date, E^3 comprises data from 41 studies with a range of ophthalmic data on approximately 170,000 individuals from population-based and other studies (case-control, cases only, randomized trials).[27] The present study was based on the fourteen E^3 population-based studies that collected best-corrected visual acuity (BCVA) data (n=70,723). Studies in the E^3 consortium were eligible for inclusion in this analysis if they were population-based, and had available data on BCVA, together with sex, age at measurement, and year of measurement.

As described in Table 1, participants included in this meta-analysis were mainly of middle to late age. Because only few studies included subjects younger than 55 years, we estimated prevalence of visual impairment and blindness only in subjects above this age. Visual acuity measurements were performed between 1991 and 2012. Designs and methods of included studies are described in Supplementary Online material (available at aaojournal.org). All studies adhered to the tenets of the Declaration of Helsinki, and relevant local ethical committee approvals with specific study consent were obtained.

Demographic and outcome variables

All included studies measured distance visual acuity (mostly using Snellen or Early Treatment of Diabetic Retinopathy Study (ETDRS) charts), with optimal refractive correction. Definitions of visual impairment and blindness vary in the literature. According to the WHO, moderate to severe visual impairment is defined as a visual acuity in the better eye <6/18 but ≥3/60 while blindness is defined as a visual acuity <3/60. By contrast, in the United States, the threshold for visual impairment is 20/40. In order to be as comparable as possible with previous studies and use all available data in the participating studies, we used the following definitions of visual impairment and blindness:

- Non-refractive visual impairment (WHO standard): BCVA<6/18 (or 20/60) in better eye
- Non-refractive visual impairment (US standard): BCVA<6/12 (or 20/40) in better eye
- Non-refractive blindness: BCVA<3/60 (or 20/400) in better eye

Differences in visual impairment by age (in ten year age bands from 55-64 years to ≥85 years), sex, time period (1991-2006 and 2007-2012, using the median of study periods), and geographical European region were examined. Countries were divided into three regions (Northern, Western, and Southern Europe) according to the United Nations Geoscheme [28]. No data were available from Eastern Europe.

Statistical analysis

For each visual endpoint, the investigators from each study provided the number of individuals stratified by sex and age group (55-64 years, 65-74 years, 75-84 years, 85 years or older). Random effects meta-analyses were performed to estimate prevalence rates. Random effects modeling was chosen over a fixed effects model, to take into account heterogeneity in study design characteristics. Subgroups with less than 50 observations were excluded from the analyses.

We first evaluated the variation in prevalence of non-refractive visual impairment and blindness with sex, time period, and geographical area. Since non-refractive visual impairment and blindness strongly vary with age and the age range was quite different among studies, we estimated age-standardized prevalence rates for all aged ≥ 55 years, using the following steps: firstly, for each stratum of sex, period, and geographical area, prevalence rates were estimated using random-effect meta-analyses in each age group (55-64 years, 65-74 years, 75-84 years, 85 years or older). Secondly, an age-standardization to age-specific European population was performed using the European Standard Population 2010 [29]. This enabled prevalence estimates that are representative for the European population, with appropriate weighting to the age demographic distribution of Europe. Subsequently, random effects meta-analyses were performed with stratification by age, sex and time-period.

Finally, in order to estimate the numbers of people affected by visual impairment and blindness, we applied the age- and period-specific prevalence rates to the population of European high-income countries, as defined by the GBD (Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom).[25] Population estimates were obtained from Eurostat. To obtain the estimates of numbers of people affected by visual impairment and blindness for the year 2000, we applied prevalence estimates of visual impairment and blindness for the 1991-2006 period to the Eurostat estimates of population for year 2000. Similarly, for the year 2010, we applied visual impairment and blindness prevalence estimates for the 2007-2012 period to the Eurostat population estimates for year 2010.

Statistical analysis was performed using R (R Development Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Fourteen studies were included in the statistical analysis (Table 1). They were conducted between 1991 and 2012 and included 70,723 participants. Age-specific prevalence estimates of the different visual endpoints in the participating studies are presented in Figure 1. The prevalence of non-refractive visual impairment strongly increased with age in all studies. For non-refractive blindness, increasing prevalence with age was not so obvious in some studies, but this was mainly due to low number of affected subjects, particularly in the older age groups. A significant inter-study variability in age-specific prevalence estimates was observed, again especially in the older age groups.

In Table 2, we estimated age-standardized prevalence rates of visual endpoints according to several factors (sex, period of eye examination, and geographical area). Prevalence of all visual endpoints tended to be somewhat higher in women, but the confidence intervals were largely overlapping with those of men. Age-standardized prevalence rates of all visual endpoints were much lower in the most recent time period (2007-2012) in comparison to the older studies (1991-2006). Indeed, the prevalence of non-refractive visual impairment (WHO standard) decreased from 2.22% to 0.83% (p=0.02). As shown in Figure 2, the differences were more pronounced in the older participants, and particularly striking in individuals aged 85 years or more: prevalence of non-refractive visual impairment (WHO standard) was 15.69 % before 2006 and less than 4.39% after 2006. Similarly, in this age group, prevalence of non-refractive blindness was about 3.26% before 2006 and 0.82% after 2006. By contrast, we observed no clear difference of prevalence of visual impairment and blindness between Northern, Western and Southern Europe (for instance, for non-refractive visual impairment 1.64 %, 1.55 % and 1.53 %, respectively, p=0.40).

In Table 3, we estimated the prevalence rates and their 95% confidence intervals, for each age- and sex-strata in 1991-2006 and in 2007-2012. Women showed higher prevalence rates of all visual endpoints in studies performed before 2006, in particular in the oldest-old (for instance, for non-refractive visual impairment, 21.45 % versus 13.11% in men, p=0.08). However, the difference was less pronounced in the more recent studies, with very similar prevalence rates in men and women in most age categories (for instance, for non-refractive visual impairment in the 85+ age category, 3.93% versus 4.03% in men, p=0.40).

In Table 4, we estimated the total number of inhabitants of European high income countries, affected by non-refractive visual impairment and blindness, in 2000 and 2010. Although the total number of subjects aged 55 years or more increased from 106 million in 2000 to 123 million in 2010, the number of subjects affected by non-refractive visual impairment decreased from 2.5 million to 1.2 million (5.2 million to 3.8 million when using the US standard). Similar decreases were observed for non-refractive blindness (584,000 to 170,000).

DISCUSSION

This study, which summarizes published and unpublished data from 14 studies performed in Europe from 1991 to 2012, provides evidence for a major decrease in the prevalence of non-refractive visual impairment and blindness in older Europeans in recent years. The age-standardized prevalence of non-refractive visual impairment in people aged 55 years or older decreased from 2.22% in 1991-2006, to 0.83% in 2007-2012. It tended to be higher in women than men in 1991-2006 (2.67% versus 1.88%), but not in 2007-2012 (0.87% versus 0.88%). No differences were observed according to geographical area. The projected numbers of affected older inhabitants in European high-income countries decreased from 2.5 million affected subjects in 2000 to 1.2 million in 2010.

In a meta-analysis of population-based studies from high-income countries (including United States, Australia, and Europe) performed in the 1990's, the prevalence rates for non-refractive visual impairment according to US standards (BCVA<20/40) were very similar to our estimates, varying from 0.56% in subjects aged 55 to 59 years to 23.73 % in subjects 80 years or older[16] (in comparison with 0.72 % in subjects aged 55-64 years to 28.95% in those age 85 years or more for the 1991-2006 period in the present study). In the National Health and Nutrition Examination Study (NHANES), the prevalence of non-refractive visual impairment (BCVA<20/40) in non-Hispanic whites aged 60 years or more was 3.9% (95% CI: 3.3 %-4.6 %) in 1999-2002, increasing to 4.5 % (95 % CI: 3.6%-5.3 %) in 2006-2008.[19] We observed a similar estimate in 1991-2006 (4.68 %, 95 % CI:2.68%-6.68%) for the

period 1991-2006, with largely overlapping confidence intervals, but a lower estimate in 2007-2012 (2.86%, 95% CI: 1.52%-4.20%).[19] This difference might be due to different temporal trends in Europe and the United States (with stability or even increase in the United States, contrasting with decrease in Europe) or to the fact that the decrease in prevalence of non-refractive visual impairment has happened after 2008, and thus was not observed in NHANES. To our knowledge, there are no available estimates of the prevalence of visual impairment in the United States after 2008. However, the GBD meta-analysis is also in favor of a decreasing prevalence of visual impairment in Northern America (from 3.5% in 1990 to 2.5% in 2010 for presenting visual acuity (PVA)<20/60).[26]

The results of the GBD meta-analysis are not directly comparable to the present study, since they were based on presenting visual acuity (PVA), thus including visual impairment due to refractive errors. However, the temporal trends were similar to our study. Indeed, in the GBD study, the prevalence of visual impairment and blindness (PVA<20/60 and PVA<20/400, respectively) decreased worldwide from 1990 to 2010.[25] This was in particular the case in European high-income countries, with a prevalence of visual impairment in subjects aged 50 years or more estimated at 6.2% (95% confidence interval (CI): 4.3%- 9.5%) in 1990 and 3.9% (95% CI: 2.8%- 6.6%) in 2010.[26] Since they estimated that 47% of visual impairment was due to refractive errors at both time points, their estimates appear somewhat higher than ours (2.22% and 0.83% for non-refractive visual impairment and blindness, respectively).

In the present study, the prevalence of non-refractive visual impairment was also halved in the most recent period (2.22% in 1991-2006 compared with 0.83% in 2007-2012). This suggests that visual impairment due to eye diseases has decreased with time. Unfortunately, causes of visual impairment and blindness were available only in some of the included studies, mainly because of incomplete eye examinations in many studies (in particular absence of assessment of lens opacities, impeding the diagnosis of cataract, and absence of visual field testing, impeding the diagnosis of glaucoma, which are leading causes of visual impairment). The decrease in non-refractive visual impairment is most

probably due to improvement in ophthalmological care over the last 20 years, with an easier access to eye care professionals in most European countries and a better reimbursement of medical expenses. In particular, surgical procedures for cataract surgery, and intraocular lenses, have improved over the last 20 years, increasing its availability, safety, and results in terms of visual acuity. Indeed, the proportion of visual impairment due to cataract has been reported to decrease in the last 20 years, worldwide, and in particular in industrialized countries.[14] Moreover, new ocular therapies have been developed in this period, including intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents for exudative macular diseases (neovascular AMD, diabetic macular edema, and macular edema due to retinal vein occlusion), which were introduced in 2006.[30-32] These therapies have led to major improvements in the visual prognosis of these diseases, and most probably contribute to a decrease in the overall prevalence of visual impairment.[34,35] For instance, a decrease of 50 % of the incidence of blindness due to AMD has been reported in Denmark, mainly after the introduction of intravitreal therapies for AMD in 2006.[33]

Finally, a decrease in the prevalence of eye diseases themselves may have contributed to a decrease in the prevalence of visual impairment. Indeed, it is now clear that the prevalence of diabetic retinopathy, and diabetic macular edema has decreased after year 2000, probably because of improvements in the management of diabetes (although this might be partly compensated by an increase in the prevalence of diabetes itself).[34] Two American studies, and a meta-analysis in Europe, based on the E3 consortium, have also suggested that the prevalence of AMD may be lower in new generations. [35-37]

Similar trends have been observed in the decrease of the prevalence of other age-related disorders, in particular dementia.[38-40] This suggests that recent generations are aging differently, which is probably due to multiple causes, such as changes in education, living conditions, lifestyle habits (smoking, nutrition, physical activity), and medical care. In particular, generations born after World War II, which are now entering old age, have experienced quite different living and nutritional

conditions than those born before, and may age differently. While it is usually projected that the number of disabled older individuals will dramatically grow in future years because of the aging population, these recent reports, including ours, suggest that these projections may be over-pessimistic. In this changing environment, epidemiological studies need to be repeated in order to monitor the trends in the prevalence of age-related disorders and related disability.

Similarly to other reports, women tended to have higher age-standardized prevalence rates of visual impairment and blindness, although this was mainly observed in the first time period (1991-2006). In the GBD meta-analysis, the prevalence of visual impairment was higher in women than in men in all world regions.[25] In the NHANES study, women had higher prevalence rates of visual impairment, both in 1999-2002 (1.5% versus 1.2% for males) and in 2006-2008 (1.9% versus 1.5%), but these differences did not reach statistical significance after adjustment for age, ethnicity, poverty, education, health insurance, and diabetes. Reasons for these potential differences in visual impairment among men and women are unclear, and the differences appear to have decreased in the more recent years in Europe.

The E3 consortium has provided a large data set to meta-analyze temporal trends for prevalence of visual impairment across Europe. One of the strengths is that this meta-analysis was built not only on published data, but also on unpublished data, which have not been included in previous estimates. The size of the dataset is much larger than in previous meta-analyses of European subjects, in particular for the most recent time period (2007-2012). For instance, the GBD meta-analysis included only 2 European studies conducted in this time period, both performed in Spain and totaling 1600 participants, while for the same time period, the present-meta-analysis included 6 studies from 7 European countries, totaling more than 36,000 participants. The estimates were also derived from raw data provided by each study following standardized procedures, in particular in the definition of the different visual endpoints.

Limitations of this consortium meta-analysis include heterogeneity between studies. Contributing studies inherently differed in study design and cohort sampling. To overcome this, we performed a random-effect rather than a fixed-effect meta-analysis, assuming no different true effect between studies. There are also differences between European countries in terms of urbanization, economy, social class, education and lifestyle, which are known to influence eye diseases. Data on these variables at an individual or study-specific level were not uniformly available, and therefore could not be included in the present study.

Representativeness of the population samples is probably also heterogeneous among studies. In order to assess whether the lower prevalence rates observed in the most recent studies might be due to a lower representativeness of those studies, we performed analyses limited to the 3 most representative studies of the 2007-2012 period (Rotterdam III, Tromsø 6th, and Coimbra Eye Study). Prevalence of non-refractive visual impairment was similar in this subgroup (1.17%, 95% CI: 0.66% - 1.67%) as in the main analysis for the 2007-2012 period (0.83%, 95% CI: 0.38%-1.28%), and lower than in the studies performed in 1991-2006 (2.22%, 95% CI: 1.34%-3.10%).

While the E3 consortium strives to include a maximum of European research groups involved in ophthalmic epidemiology, participating studies were mostly from European high-income countries, while no studies from Central and Eastern Europe could be included, except for a small sample from Estonia. To our knowledge, only very few epidemiological studies including measurements of visual acuity have been conducted in Central and Eastern Europe. For instance, only three such studies were included in the GBD meta-analysis (including the sample from Estonia which is also included in our meta-analysis).[26] However, the available data suggest that the prevalence of visual impairment and blindness may be higher in Central and Eastern Europe than in European high-income countries.[26] Thus, we decided not to extrapolate our findings to those areas of Europe. Epidemiological studies conducted in these areas of Europe would be particularly informative.

In addition, as shown in Table 1, the majority of participating studies collected data only in subjects aged 55 years or more. We therefore could not estimate the prevalence of visual impairment below

this age. Finally, most participating studies included only measures of best-corrected visual acuity, but not of presenting visual impairment, so it was only possible to estimate the prevalence of non-refractive visual impairment. The causes of visual impairment were also generally not available. Future European epidemiological studies should strive to include measures of presenting visual acuity and to determine the causes of visual impairment, in order to give a more complete description of the epidemiology of visual impairment in Europe. In particular, uncorrected refractive errors represent a major cause of visual impairment and blindness worldwide, including in Europe [14].

In conclusion, this meta-analysis supports a decrease in the prevalence and numbers of older Europeans affected by non-refractive visual impairment and blindness in the last twenty years. This decrease may be due to major improvements in eye care and/or to a generation effect on eye disease incidence. These findings underline the need for continuing epidemiological monitoring of the temporal trends of ocular health in Europe.

Author contributions:

CD led the statistical analysis and drafted the manuscript. MLG performed the statistical analyses. All authors contributed to study design, data collection, data interpretation, revised the manuscript for important intellectual content and approved the final version of the manuscript.

REFERENCES

1. McKean-Cowdin R, Varma R, Hays RD, et al. Longitudinal changes in visual acuity and health-related quality of life: the Los Angeles Latino Eye study. *Ophthalmology*. 2010;117:1900-1907, 1907 e1901.
2. Seland JH, Vingerling JR, Augood CA, et al. Visual impairment and quality of life in the older European population, the EUREYE study. *Acta Ophthalmol*. 2011;89:608-613.
3. Lam BL, Christ SL, Zheng DD, et al. Longitudinal Relationships among Visual Acuity and Tasks of Everyday Life: The Salisbury Eye Evaluation Study. *Invest Ophthalmol Vis Sci*. 2013;54:193-200.
4. Daien V, Peres K, Villain M, et al. Visual acuity thresholds associated with activity limitations in the elderly. The Pathologies Oculaires Liees a l'Age study. *Acta Ophthalmol*. 2014;92:e500-506.
5. Carriere I, Delcourt C, Daien V, et al. A prospective study of the bi-directional association between vision loss and depression in the elderly. *J Affect Disord*. 2013;151:164-170.

6. Lamoureux EL, Fenwick E, Moore K, et al. Impact of the severity of distance and near-vision impairment on depression and vision-specific quality of life in older people living in residential care. *Invest Ophthalmol Vis Sci*. 2009;50:4103-4109.
7. Patino CM, McKean-Cowdin R, Azen SP, et al. Central and peripheral visual impairment and the risk of falls and falls with injury. *Ophthalmology*. 2010;117:199-206 e191.
8. Yip JL, Khawaja AP, Broadway D, et al. Visual acuity, self-reported vision and falls in the EPIC-Norfolk Eye study. *Br J Ophthalmol*. 2014;98:377-382.
9. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1545-1602.
10. Chakravarthy U, Biundo E, Saka RO, et al. The Economic Impact of Blindness in Europe. *Ophthalmic Epidemiol*. 2017;24:239-247.
11. Gordois A, Cutler H, Pezzullo L, et al. An estimation of the worldwide economic and health burden of visual impairment. *Glob Public Health*. 2012;7:465-481.
12. Organization WH. Action plan for the prevention of avoidable blindness and vision impairment, 2009-2013. World Health Organization, 2010.
13. Organization WH. Universal eye health: a global action plan 2014-2019: World Health Organization, 2013.
14. Bourne RR, Stevens GA, White RA, et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. *Lancet Glob Health*. 2013;1:e339-349.
15. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. *Br J Ophthalmol*. 2012;96:614-618.
16. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. *Arch. Ophthalmol.* 2004;122:477-485.
17. Lee DJ, Gomez Marin O, Lam BL, et al. Trends in visual acuity impairment in US adults: the 1986-1995 National Health Interview Survey. *Arch. Ophthalmol.* 2004;122:506-509.
18. Vitale S, Cotch MF, Sperduto RD. Prevalence of visual impairment in the United States. *JAMA*. 2006;295:2158-2163.
19. Ko F, Vitale S, Chou CF, et al. Prevalence of nonrefractive visual impairment in US adults and associated risk factors, 1999-2002 and 2005-2008. *JAMA*. 2012;308:2361-2368.
20. Klaver CCW, Wolfs RCW, Vingerling JR, et al. Age-specific prevalence and causes of blindness and visual impairment in an older population: The Rotterdam Study. *Arch. Ophthalmol.* 1998;116:653-658.
21. Evans JR, Fletcher AE, Wormald RP, et al. Prevalence of visual impairment in people aged 75 years and older in Britain: results from the MRC trial of assessment and management of older people in the community. *Br J Ophthalmol*. 2002;86:795-800.
22. Gunnlaugsdottir E, Arnarsson A, Jonasson F. Prevalence and causes of visual impairment and blindness in Icelanders aged 50 years and older: the Reykjavik Eye Study. *Acta Ophthalmol*. 2008;86:778-785.
23. Khawaja AP, Chan MP, Hayat S, et al. The EPIC-Norfolk Eye Study: rationale, methods and a cross-sectional analysis of visual impairment in a population-based cohort. *BMJ Open*. 2013;3.
24. Bertelsen G, Erke MG, von Hanno T, et al. The Tromso Eye Study: study design, methodology and results on visual acuity and refractive errors. *Acta Ophthalmol*. 2013;91:635-642.
25. Stevens GA, White RA, Flaxman SR, et al. Global prevalence of vision impairment and blindness: magnitude and temporal trends, 1990-2010. *Ophthalmology*. 2013;120:2377-2384.
26. Bourne RR, Jonas JB, Flaxman SR, et al. Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe: 1990-2010. *Br J Ophthalmol*. 2014;98:629-638.
27. Delcourt C, Korobelnik JF, Buitendijk GH, et al. Ophthalmic epidemiology in Europe: the "European Eye Epidemiology" (E3) consortium. *Eur J Epidemiol*. 2016;31:197-210.
28. Division UNS. Standard Country and Area Codes. *https://unstats.un.org/unsd/methods/m49/m49regin.htm (Accessed 4/3/2014)*.

29. Eurostat EC. Revision of the European Standard Population: Report of Eurostat's task force. *Eurostat Methodologies and working papers*. 2013.
30. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419-1431.
31. Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117:1064-1077 e1035.
32. Korobelnik JF, Holz FG, Roider J, et al. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. *Ophthalmology*. 2014;121:202-208.
33. Bloch SB, Larsen M, Munch IC. Incidence of legal blindness from age-related macular degeneration in denmark: year 2000 to 2010. *Am J Ophthalmol*. 2012;153:209-213 e202.
34. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35:556-564.
35. Klein R, Knudtson MD, Lee KE, et al. Age-period-cohort effect on the incidence of age-related macular degeneration: the Beaver Dam Eye Study. *Ophthalmology*. 2008;115:1460-1467.
36. Klein R, Chou CF, Klein BE, et al. Prevalence of age-related macular degeneration in the US population. *Arch Ophthalmol*. 2011;129:75-80.
37. Colijn JM, Buitendijk GHS, Prokofyeva E, et al. Prevalence of Age-Related Macular Degeneration in Europe: The Past and the Future. *Ophthalmology*. 2017;124:1753-1763.
38. Matthews FE, Arthur A, Barnes LE, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet*. 2013;382:1405-1412.
39. Grasset L, Brayne C, Joly P, et al. Trends in dementia incidence: Evolution over a 10-year period in France. *Alzheimers Dement*. 2016;12:272-280.
40. Satizabal CL, Beiser AS, Chouraki V, et al. Incidence of Dementia over Three Decades in the Framingham Heart Study. *N Engl J Med*. 2016;374:523-532.

Figures legends:

Figure 1. Prevalence (in %) of non-refractive visual impairment according to age, in studies participating to the E3 consortium (A: non-refractive visual impairment (best-corrected visual acuity<20/60); B: non-refractive visual impairment (best-corrected visual acuity<20/40); C: non-refractive blindness (best-corrected visual acuity<20/400))

Figure 2. Prevalence (in %) of non-refractive visual impairment according to age and period (non refractive visual impairment (A: non-refractive visual impairment (best-corrected visual acuity<20/60); B: non-refractive visual impairment (best-corrected visual acuity<20/40); C: non-refractive blindness (best-corrected visual acuity<20/400))