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NEW STUDY

Ophthalmic epidemiology in Europe: the "European Eye Epidemiology" (E3) consortium

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Abstract The European Eye Epidemiology (E3) consortium is a recently formed consortium of 29 groups from 12 European countries. It already comprises 21 population-based studies and 20 other studies (case–control, cases only, randomized trials), providing ophthalmological data on approximately 170,000 European participants. The aim of the consortium is to promote and sustain collaboration and sharing of data and knowledge in the field of ophthalmic epidemiology in Europe, with particular focus on the harmonization of methods for future research, estimation and projection of frequency and impact of visual outcomes in European populations (including temporal trends and European subregions), identification of risk factors and pathways for eye diseases (lifestyle, vascular and metabolic factors, genetics, epigenetics and biomarkers) and development and validation of prediction models for eye diseases. Coordinating these existing data will allow a detailed study of the risk factors and consequences of eye diseases and visual impairment, including study of international geographical variation which is not possible in individual studies. It is expected that collaborative work on these existing data will provide additional knowledge, despite the fact that the risk factors and the methods for collecting them differ somewhat among the participating studies. Most studies also include biobanks of various biological samples, which will enable identification of biomarkers to detect and predict occurrence and progression of eye diseases. This article outlines the rationale of

On behalf of the European Eye Epidemiology (E3) consortium.

Please see "Appendix" section for European Eye Epidemiology (E3) consortium members.

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the consortium, its design and presents a summary of the methodology.

Keywords Epidemiology · Ophthalmology · Eye diseases · Prevalence · Risk factors · Europe

Introduction

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]. The costs of lost productivity and of rehabilitation and education of the blind constitute a considerable economic burden for the individual, the family and society. Vision loss also incurs both direct health care costs and indirect costs of lost productivity, welfare and informal care. The global annual cost of visual impairment was recently estimated to be 3000 billion US dollars (563 billion US dollars for Europe) [9].

Worldwide and in Europe, the major causes of visual impairment in adults currently are age-related eye diseases (cataract, age-related macular degeneration (AMD), glaucoma and diabetic retinopathy), together with uncorrected refractive errors (myopia, hyperopia, astigmatism) and presbyopia [10, 11]. Globally, 65 % of visually impaired subjects and 82 % of the blind are aged 50 years or more [10]. Thus, the number of visually impaired people will increase worldwide with the ongoing aging demographic, unless preventive and therapeutic strategies are implemented. Since 1999, prevention of visual impairment and blindness is a priority of the World Health Organization, 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].

Indeed, an increasing proportion of visual impairment is potentially avoidable, due to improvements in treatments for many blinding disorders. These include cataract surgery, intraocular (IOP) lowering therapies and surgical procedures, laser therapies, and development of anti-angiogenic intravitreal therapies. Together with the advances in retinal imaging, intravitreal therapies have revolutionized the management of retinal diseases in the clinical setting [14]. However, despite these improvements, visual impairment cannot always be prevented, due to late presentation of patients, variability in treatment responsiveness, or the development of untreatable complications.

In conjunction with medical progress in the management of eye diseases, the public has been informed on modifiable risk factors by the large epidemiological studies of recent

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decades. In particular, smoking is now recognized as a major risk factor for cataract [15–19], AMD [20–25] and retinal vein occlusion [24, 26]. Ultraviolet light exposure is a recognized risk factor for cataract [15, 27–31] and pterygium, [32, 33] and has been shown to be a risk factor for AMD in those with low blood level of key antioxidant vitamins [34]. Indeed, the role of dietary antioxidants (including lutein and zeaxanthin) has been investigated in many eye disorders [35–46]. There is also growing literature on the potential role of other nutritional factors (in particular omega 3 fatty acids) in the etiology of age-related eye diseases [41, 47–58]. Diabetes is associated with specific retinal complications such as diabetic retinopathy and diabetic macular edema, and is independently associated with an increased risk for cataract [17, 19, 59]. Improved prevention and management of diabetes thus has important potential consequences for ocular health. These lifestyle risk factors (smoking, ultraviolet exposure, outdoor activity, nutrition, exercise, obesity, and diabetes) not only relate to eye disorders, they also bear a great risk of other major chronic diseases such as cardiovascular diseases and cancers. They have been a focus for national and international public health programs and the arousal of public awareness may have impacted the prevalence of age-related eye diseases in Europe, and the related visual impairment. However, detailed data on temporal trends in Europe are scarce.

Ophthalmic epidemiology in Europe

Understanding the population and the epidemiology of common diseases is essential for planning future healthcare provision [60]. As the European population ages and environmental risk factors change, thorough epidemiological research is necessary to ensure sufficient medical care, evidence-based public health screening and efficient use of medical resources.

In the past twenty years, ophthalmic epidemiology has successfully identified genetic and environmental risk factors for eye diseases and visual impairment. Before 2000, few specific studies were undertaken in Europe, limiting the knowledge on visual impairment and eye diseases. Since then, many studies on eye health involving multiple European countries and totaling more than 170,000 participants have been performed. Most recently, very large studies have been undertaken, such as the UK Biobank study, the largest prospective study of health and disease (118,000 subjects with detailed ophthalmic examination, http://www.ukbiobank.ac.uk/) or the Constances study in France (currently 41,000 with ophthalmological data, planned 200,000) [61].

Overall, these studies have provided estimates of the frequency of visual impairment and eye diseases in European countries, and have had a major role in the identification of their genetic and environmental risk factors. However, the epidemiological data provided by these numerous studies have not been related to the European continent as a whole. The E3 collaboration aims to provide robust and precise estimates of prevalence and risk factors for visually impairing diseases across Europe. We believe this will deliver a strong and coherent public health message to populations across Europe and national governments. It will also enable examination of temporal trends and differences in European sub-regions in prevalence of eye conditions. Projections of frequency of eye diseases and visual impairment will allow a better planning of their prevention and treatment in the future.

Aside from these general epidemiological issues, ophthalmic epidemiology has been faced with methodological challenges. The major technological advances in eye

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imaging, which have profoundly influenced clinical practice, have only been implemented in more recent epidemiological studies. In particular, optical coherence tomography (OCT) has changed eye epidemiology, for it allows for noninvasive cross-sectional imaging of retinal layers, facilitating the diagnosis of structural changes in diseases such as age-related macular degeneration, vascular occlusions and diabetic retinopathy. Innovative eye imaging techniques are now commonly used in clinical practice but international classification systems of procedures and interpretation of images to standardize epidemiological data collection is currently lacking. The E3 collaboration strives to develop such international classification systems for use in future epidemiological studies. It may also help identifying and validating novel markers based on these imaging techniques, which could predict occurrence of eye diseases, or represent surrogate endpoints in future clinical trials.

There have also been major advances in the understanding of the molecular pathophysiological pathways of the major eye diseases. Many genetic polymorphisms associated with age-related eye diseases have been identified in the last decade, mainly through genome-wide association studies. Large international consortia (such as AMD Genomics Consortium for AMD [62], CREAM for refractive error and myopia [63], and IGGC for glaucoma [64]) identified numerous genetic risk variants for these diseases by meta-analysis of thousands of study subjects. These consortia included studies from US, Asia, Australia, and Europe. New genetic and statistical developments (1000 genome analysis, exome platforms and sequencing) are currently paving the way for more detailed analyses of the genetic loci and possible rare variants involved. The latter in particular are likely to be population-specific. The consorted action of E3 will provide the required statistical power which no individual studies have, given the generally small effect sizes. In addition, these comprehensive genetic analyses will improve current models for prediction of disease [65] and enable development of prediction models specific for European populations.

Finally, although progress has been made in identification of lifestyle risk factors for ocular diseases, detection of specific biochemical biomarkers for diagnosis and prognosis has been less successful. Biomarkers may be circulating (plasma, serum, red blood cells, leukocytes) or tissue-specific (tears, aqueous humor, vitreous) and include inflammatory markers, lipid molecules, peptides or

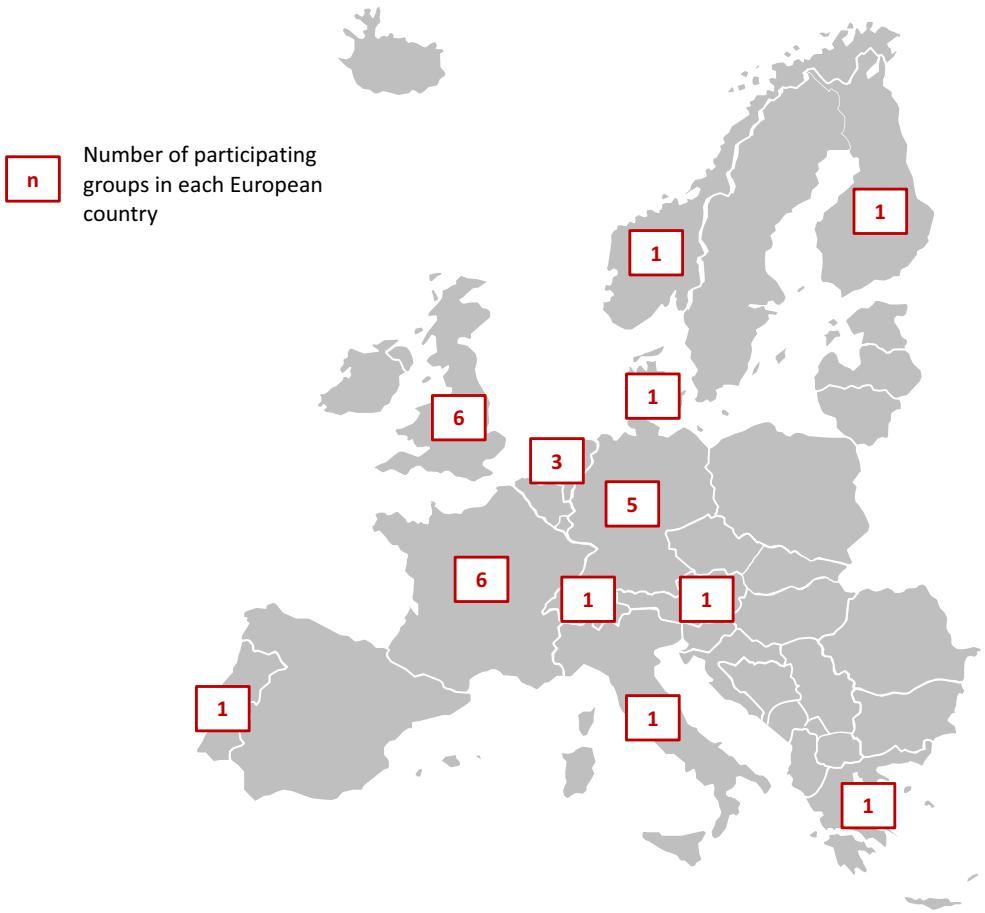

Fig. 1 Map of groups participating in the E3 consortium (May 2015)

Table 1 Population-based studies participating in the E3 consortium

Study name	Country	Period of first eye examination	Age range	Number of subjects with eye examination	Prospective study?
1958 British Birth cohort	UK	2002	44–45	9330	Yes
Young Finns Study	Finland	2010	33–48	1684	Yes
Rotterdam Study I	Netherlands	1990–1993	55+	6913	Yes
Twins UK	UK	1992	18+	6247	Yes
MRC Older People Study	UK	1995–1998	75+	14,593	For mortality outcomes
POLA	France	1995–1998	60+	2584	Yes
Tromsø Eye Study	Norway	2001	40+	6540	Yes
Rotterdam Study II	Netherlands	2000–2001	55+	3011	Yes
Eureye	Norway, Estonia, UK, France, Italy, Greece, Spain	2001–2002	65+	4753	No
Thessaloniki Eye Study	Greece	2000–2005	60+	2554	Yes
ERF	Netherlands	2002	18+	2940	Yes
KORA	Germany	2004–2005	35+	3078	No
PAMDI	Italy	2005–2006	60+	1162	No
Epic-Norfolk	UK	2004–2011	45+	8623	No
Alienor	France	2006–2008	73+	963	Yes
Rotterdam Study III	Netherlands	2006–2008	45+	3682	Yes
Gutenberg Health Study	Germany	2007–ongoing	35–74	14,700	Yes
Coimbra Eye Study	Portugal	2009–2013	55+	6023	No
Montrachet	France	2009–2012	75+	1153	Yes
Generation R	Netherlands	Ongoing	0+	~6000	Yes
NICOLA	UK	Ongoing	50+	~5500	Yes
Total				~112,000	

proteins. Recent developments in analytical tools such as metabolomics, proteomics or lipidomics have opened up new avenues. To be considered reliable surrogate endpoints, biomarkers must fulfill several criteria in terms of robustness, reliability, precision, reproducibility, sensitivity and specificity. Insufficient sample sizes have been barriers to identify subtle changes in biochemical markers, hampering valid comparisons between studies. Standardization of methodologies and pooling of biological samples across European studies may enable more rapid progress in this area.

Pooling of existing data from European epidemiological studies will provide a major research resource, integrating genetic and biochemical biomarkers. We aim to translate these data into novel epidemiological insights that convey important messages to the public, medical practitioners and policy makers for lifestyle modification and other preventive strategies, with the ultimate aim of preventing visual impairment and blindness. Finally, pooling of data from different European epidemiological datasets will facilitate powerful studies to predict future magnitude and impact of visual impairment in Europe.

Scope of the European Eye Epidemiology (E3) consortium

The aim of the consortium is to promote ophthalmic epidemiology in Europe, by exchange of scientific knowledge and methodology, in particular for:

- harmonization of methods (classification of ocular outcomes, measures of risk factors)
- estimation of frequency and impact of visual outcomes in European populations (visual impairment, quality of life, eye diseases)
- identification of geographic differences in the prevalence and incidence of ophthalmic diseases and conditions across Europe
- projections of frequency of visual impairment and eye diseases in European populations
- identification of risk factors and pathways for eye diseases (lifestyle, vascular and metabolic factors, genetics, biomarkers)
- development and validation of prediction models for eye diseases

Table 2 Other studies participating in the E3 consortium

Study name	Country	Period of eye examination	Age range	Number of subjects	Type of study	Types of cases
Danish cohort of pediatric diabetes 1987	Denmark	1995–2011	28–42	324	Longitudinal study	Diabetes
AMRO-NL	Netherlands	1998–2005	55+	1194	Hospital based-cohort	Glaucoma AMD
Belfast	UK	2001	50+	402	Case–control	AMD
Guernsey AMD case cohort study	UK	2003	50+	371	Case–control	AMD
Southampton Rod-cone Dystrophies	UK	2003	10+	143	Case only	Rod-cone dystrophy
Southampton POAG	UK	2003	40+	1618	Case only	Glaucoma
MARS	Germany	2003–2010	60–80	1060	Hospital-based cohort	AMD
Fyns Diabetes Database	Denmark	2003–2015	0+	22,089	Case only	Diabetes
Creteil Study	France	2005	55+	2081	Case–control	AMD
CARMA	UK/Ireland	2005	55+	430	Randomized clinical trial	AMD
EUGENDA	Netherlands/ Germany	2006	50+	4800	Case–control	AMD
Southampton nystagmus	UK	2006	0+	244	Case–control	Nystagmus
Early Observational Markers Study	UK/ Italy/ Portugal	2007	50+	105	Longitudinal study	AMD
CIC XV XX	France	2008	55+	794	Case–control	AMD
IVAN Study	UK	2008	50+	608	Longitudinal study	AMD
Southampton paediatric eye diseases	UK	2008	0–16	474	Case–control	Paediatric eye diseases
Southampton AMD/glaucoma case–control Study	UK	2009	50+	56	Case–control	AMD/glaucoma
MYST	Netherlands	2009–2012	25+	1200	Case–control	High myopes
Southampton Liver Transplant	UK	2010	50+	241	Cases only	Liver transplant
Coimbra-RD	Portugal	2011–2012	40+	22,658	Cases only	Diabetes
Total				60,892		

building capacity and expertise in ophthalmic and genetic epidemiology in Europe and translating expertise to young researchers

communicating findings and recommendations to the medical community, policy makers and the public

These aims will be supported by assembling background information from participating studies, developing a plan for harmonization of core exposure and outcome variables, and pooling of data, effectively increasing sample size to yield statistically powered and robust data analyses.

Currently participating studies

As of May 2015, 29 groups from 12 European countries are participating in the E3 consortium (Fig. 1). European research groups active in ophthalmic epidemiology have been considered eligible for membership of the Consortium. As seen on Fig. 1, the majority of participating studies originate from high income European countries; only one centre (from the EUREYE study) is situated within a former communist country. To our knowledge, few epidemiological studies have been performed in Eastern Europe [66].

Overall, the E3 Consortium includes 21 population-based studies in ophthalmic epidemiology, of which 16 are prospective (Table 1), and 20 other studies, including case–control studies, case only studies and randomized clinical trials (Table 2). Overall, these studies collected ophthalmological data in >170,000 European subjects. As new studies are being performed in Europe, we anticipate that the number of studies will be growing in the next years. In particular, collaboration with the UK Biobank study (http://www.ukbiobank.ac.uk/) and the Constances study is being considered [61].

The age range of participants varied, but most studies included subjects older than 50 years, while few studies include young subjects. Phenotyping was performed

Table 3 Ocular endpoints available in population-based studies

Study name	Vision	Visual fields	Refractive errors	IOP[a]	AMD	Glaucoma	Retinal vessels	OCT examinations
1958 British Birth cohort	X		X					
Young Finns Study			X				X	
Rotterdam Study I	X	X	X	X	X	X	X	X
Twins UK			X	X	X	X	X	X
MRC Older People Study	X		X		X			
POLA	X		X	X	X		X	
Tromsø Eye Study	X		X		X		X	X
Rotterdam Study II	X	X	X	X	X			X
Eureye	X		X		X			
Thessaloniki Eye Study	X	X	X	X	X	X	X	X
ERF	X		X	X	X	X	X	
KORA			X			X		
PAMDI	X		X	X	X	X		
Epic-Norfolk	X	X	X	X	X	X		
Alienor	X		X	X	X	X	X	X
Rotterdam Study III	X	X	X	X	X	X	X	X
Gutenberg Health Study	X	X	X	X	X	X	X	X
Coimbra Eye Study	X		X	X	X			
Montrachet	X	X	X	X	X	X	X	X
Generation R	X		X				X	X
NICOLA	X		X	X	X	X	X	X

[a] Intraocular pressure

between 1995 and 2015, and thus allow for the study of temporal trends in the prevalence of ocular disease. As shown in Table 3, a variety of ocular phenotypes have been collected in these studies. The vast majority of studies collected measurements of vision and refractive errors. Most studies also collected data on intraocular pressure, AMD and retinal vessels. A smaller number of studies included visual field examinations and diagnosis of glaucoma.

As shown in Tables 4 and 5, most of the participating studies also collected data on a variety of risk factors potentially related to ocular health, such as socio-demographic characteristics (educational level, socio-economic status), medical history and medications, quality of life and disability, lifestyle and environment (smoking, alcohol, body mass index, nutrition, physical activity), laboratory (glucose, lipids, biomarkers of inflammation, renal and liver function, nutritional biomarkers), cardiovascular (blood pressure, ankle brachial index, carotid arteries, aortic and cardiac measurements, pulsometry) and neuropsychiatric (cognitive and psychiatric testing, brain imaging) measurements, genetics and genomics determinations (specific genetic polymorphism, GWAS, ExomeCorechip or exome sequencing) as well as epigenetic determinations (microRNA and DNA methylation). Coordinating these existing data will allow an in-depth study of the risk factors and consequences of eye diseases and visual impairment, although the risk factors and the methods for collecting them somewhat differ among the participating studies. Most studies also include biobanks, which may allow measurement of new biomarkers to determine their validity in detecting and predicting occurrence and progression of eye diseases (Tables 4 and 5).

Structure of the consortium

Collaboration within the E3 consortium is defined by a Memorandum of Understanding, which has been signed by all participating teams. It is managed by an Executive Committee (with one representative for each participating institution) and a Steering Committee (constituted of the leaders of the workgroups). As of May 2015, there are ten active workgroups (Table 6). The E3 consortium is open to new members working in the field of eye epidemiology in Europe. All membership requests are examined by the Executive Committee. Meetings dedicated to the consortium to consolidate objectives and future plans are planned on a yearly basis, and have been held in Bordeaux in June 2011, 2012 and 2013, in Rome in June 2014 and in London in June 2015.

Table 4 Other collected data in participating population-based studies

Study name	Socio-demographic	Medical history	Quality of life/ disability	Lifestyle/ environment	Laboratory measurements	Cardiovascular measurements	Neuro-psychiatric measurements	Omics	Biobanks
1958 British Birth cohort	X	X	X	X	X	X		X	X
Young Finns Study	X	X	X	X	X	X	X	X	X
Rotterdam I	X	X	X	X	X	X	X	X	X
Twins UK	X	X	X	X	X	X	X	X	X
MRC Older People Study	X	X	X	X	X	X	X		
POLA	X	X	X	X	X	X			
Tromsø Eye Study	X	X	X	X	X	X	X		X
Rotterdam Study II	X	X	X	X	X	X	X	X	X
Eureye	X	X	X	X	X	X		X	X
Thessaloniki Eye Study		X		X		X		X	X
ERF	X	X		X	X	X	X	X	X
KORA	X	X	X	X		X		X	X
PAMDI	X	X	X	X	X	X			
Epic-Norfolk	X	X	X	X	X	X	X	X	X
Alienor	X	X	X	X	X	X	X	X	X
Rotterdam Study III	X	X	X	X	X	X	X	X	X
Gutenberg Health Study	X	X	X	X	X	X	X	X	X
Coimbra Eye Study		X		X	X				
Montrachet	X	X	X	X	X	X	X	X	X
Generation R	X	X		X	X	X	X	X	
NICOLA	X	X	X	X	X	X	X		X

Table 5 Other collected data in other participating studies

Study name	Socio-demographic	Medical history	Quality of life/disability	Lifestyle/ environment	Laboratory measurements	Cardiovascular measurements	Neuro-psychiatric measurements	Omics	Biobanks
Danish cohort of pediatric diabetes 1987		X		X	X	X			X
AMRO-NL	X	X		X				X	X
Belfast		X		X	X	X		X	X
Guernsey AMD study		X		X				X	X
Southampton Rod-cone Dystrophies		X		X				X	X
Southampton POAG		X		X				X	X
MARS	X	X	X	X	X	X		X	X
Creteil Study	X	X		X		X		X	X
CARMA									
EUGENDA	X	X		X	X			X	X
Southampton nystagmus		X		X					X
Fyns Diabetes DataBase		X		X	X	X			
Early Observational Markers Study				X					
IVAN Study		X		X				X	X
Southampton paediatric eye diseases		X		X					X
Southampton AMD/glaucoma case–control Study									
CIC XV XX	X	X		X					X
MYST	X	X		X				X	X
Southampton Liver Transplant		X		X				X	X
Coimbra RD									

Table 6 Active E3 workgroups (November 2014)

Workgroup	Topic	Leader
1	Visual impairment	Cécile Delcourt
2	AMD	Caroline Klaver
3	Glaucoma	Paul Foster
4	Diabetic retinopathy	Tunde Peto
5	Refractive errors	Christopher Hammond
6a	Imaging- retina	Jean-François Korobelnik
6b	Imaging-optic nerve	Nomdo Jansonius
7	Epidemiological projections	Elena Prokofyeva
8	Genetic epidemiology	Gabriëlle Buitendijk
9	Biomarkers	Ruth Hogg and Lionel Bretillon
10	Retinal vessels	Alireza Mirshahi

Harmonization of data and first activities of the consortium

One of the difficulties encountered in meta-analyses is the heterogeneity of the collected data. Some of the heterogeneity may be overcome by standardizing data analysis (using similar definitions of endpoints and similar statistical methods), while in other cases, new methods for interpreting and collecting data are needed.

A number of ocular outcomes (refractive errors, visual impairment, AMD and diabetic retinopathy) have been collected in a standardized manner in E3 participating studies owing to long-established consensus in the methods of collection and classification. Using summary data from participating studies a number of meta-analyses on the prevalence of these outcomes have been undertaken. These analyses have formed the basis for the two reports on the prevalence of refractive errors and myopia in Europe [67, 68]. Additional manuscripts are in preparation on the prevalence of visual impairment and AMD (including temporal trends and geographical variation), and an ongoing meta-analysis on the prevalence of diabetic retinopathy.

For other outcomes, a need for harmonization has been identified. In particular, standardization of macular SD-OCT examinations, and consensus on the interpretation and classification of macular diseases are needed. To address this, we have developed a new classification, for use in epidemiological studies. The manuscript describing this new classification is in preparation and has been distributed to E3 participants for use in their ongoing studies. Harmonized interpretation of SD-OCT examinations throughout European epidemiological studies should thus be soon available. Significant variability also exists among European studies with regard to the data collection and classification of glaucoma. Harmonization of existing data represents a challenge in this field.

With regard to the identification of risk factors, a meta-analysis has been conducted on the factors associated with intra-ocular pressure (including age, gender, BMI, height, blood pressure and refractive errors). Each study performed multivariate linear regression models, using a standardized statistical plan, and regression coefficients were then meta-analyzed. This paper is currently submitted.

The next step in the integration of European data will be undertaken within the Eye-Risk project, which is funded by the European Union's Horizon 2020 Research and Innovation Programme (www.eyerisk.eu). This project will explore the combined role of genetic and non-genetic risk factors for AMD. It plans to integrate individual data from E3 participating studies into a common E3 database, which will be used for data analysis. This will require harmonization of data on genetic and non-genetic risk factors (including lifestyle, nutrition, in-depth retinal imaging, circulating biomarkers). This represents a major challenge, since data on risk factors have been collected in a highly variable way in participating studies. Some additional, harmonized, data collection will most probably be necessary, in particular in the field of genetic polymorphisms and circulating biomarkers. In the future, we plan to further extend this database to other ocular endpoints, allowing for powerful, detailed analyses of risk factors of various eye diseases.

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Compliance with ethical standards

Conflict of interest C Delcourt received research grants from Laboratoires Théa and is board member for Bausch + Lomb, Laboratoires Théa and Novartis; JF Korobelnik is consultant for Alcon, Allergan, Bayer, Horus, Novartis, Roche, Théa, Zeiss; P Foster received honoraria from Carl Zeiss Meditech and Allergan (UK) and travel grants and unrestricted research grants from Alcon; A Mirshahi received research grants from Novartis and Bayer; L Bretillon received research grants from Laboratoires Horus Pharma, Laboratoires, THEA, Laboratoires Fournier/Abbott, travel grants from Laboratoires Horus Pharma, honoraria from Laboratoires Chauvin Bausch & Lomb, and is consultant for Novartis; F Topouzis received support from a project sponsor from Pfizer, Novartis, Alcon and Laboratoires Thea, honoraria for speaking at symposia from Alcon and is board member for Alcon, Bausch + Lomb, Humphrey, Zeiss, Allergan, Pfizer, Laboratoires Théa and Novartis; EH Souied is board member for Novartis, Bayer, Thea, Allergan; J Sahel is founder of Pixium Vision and Gensight Biologics and is consultant for Pixium Vision, Gensight Biologics, Sanofi Fovea, Genesignal and Vision Medecine; R Silva is member of Advisory board for Allergan, Bayer, Alimera, Novartis, THEA, Alcon. Other authors have no potential conflict of interest.

Appendix: European Eye Epidemiology (E3) consortium members

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Alain	Bron	University Hospital of Dijon	Dijon	France
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First name	Last name	Institution	City	Country
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