Aus der Klinik und Poliklinik für Augenheilkunde
des Universitätsklinikums Bonn

Direktor: Prof. Dr. med. Frank G. Holz

Epidemiologic analyses of large-scale ophthalmic datasets

Habilitationsschrift

zur Erlangung der Venia Legendi

der Hohen Medizinischen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

für das Lehrgebiet „Augenheilkunde“

Dr. med. Matthias Marten Mauschitz, PhD

Facharzt für Augenheilkunde und wissenschaftlicher Mitarbeiter an dem Universitätsklinikum Bonn

Bonn 2024

Manuscripts of this cumulative habilitation thesis:

1. Wabbels B, Fricke J, Schittkowski M, Gräf M, Lorenz B, Bau V, Nentwich MM, Atili A, Eckstein A, Sturm V, Beisse C, Sterker I, Neppert B, **Mauschitz MM**. Yokoyama procedure for esotropia associated with high myopia: real-world data from a large-scale multicentre analysis. Acta Ophthalmol. 2021 Dec;99(8):e1340-e1347. DOI: 10.1111/aos.14808
   Impact Factor: 3.30

2. **Mauschitz MM**, Lohner V, Koch A, Stöcker T, Reuter M, Holz FG, Finger RP, Breteler MMB. Retinal layer assessments as potential biomarkers for brain atrophy in the Rhineland Study. Sci Rep. 2022 Feb 17;12(1):2757. DOI: 10.1038/s41598-022-06821-4
   Impact Factor: 4.996

3. **Mauschitz MM**, Schmitz MT, Verzijden T, Schmid M, Thee EF, Colijn JM, Delcourt C, Cougnard-Grégoire A, Merle BMJ, Korobelnik JF, Gopinath B, Mitchell P, Elbaz H, Schuster AK, Wild PS, Brandl C, Stark KJ, Heid IM, Günther F, Peters A, Klaver CCW, Finger RP; European Eye Epidemiology (E3) Consortium. Physical Activity, Incidence, and Progression of Age-Related Macular Degeneration: A Multicohort Study. Am J Ophthalmol. 2022 Apr;236:99-106. DOI: 10.1016/j.ajo.2021.10.008
   Impact Factor: 5.258

4. **Mauschitz MM**, Verzijden T, Schuster AK, Elbaz H, Pfeiffer N, Khawaja A, Luben RN, Foster PJ, Rauscher FG, Wirkner K, Kirsten T, Jonas JB, Bikbov MM, Hogg R, Peto T, Cougnard-Grégoire A, Bertelsen G, Erke MG, Topouzis F, Giannoulis DA, Brandl C, Heid IM, Creuzot-Garcher CP, Gabrielle PH, Hense HW, Pauleikhoff D, Barreto P, Coimbra R, Piermarocchi S, Daien V, Holz FG, Delcourt C, Finger RP; European Eye Epidemiology (E3) Consortium. Association of lipid-lowering drugs and antidiabetic drugs with age-related macular degeneration: a meta-analysis in Europeans. Br J Ophthalmol.2023 Nov 22;107(12):1880-1886. DOI: 10.1136/bjo-2022-321985
   Impact Factor: 4.638

Median des Impact Factors (IF) im Fach Augenheilkunde (2022): 3.0

Habilitationskolloquium: 09.11.2023

Table of content

Introduction

Ophthalmic diseases are remarkably common and affect at least 2.2 billion people worldwide. (World Health Organization, 2019) From a global perspective, treatable conditions such as refractive errors and cataract play the main role, with a strongly increasing prevalence of myopia, particularly in Asian countries. (Wu et al., 2016) The current global prevalence of myopia ranges above 28% and a highly increasing prevalence is estimated to leave one out of ten persons at relevant risk of becoming blind as a result of myopia and its secondary complications (**see Study 1**). (Holden et al., 2014; Hopf and Pfeiffer, 2017)

In the Western world, mainly age-related conditions including **age-related macular degeneration** (AMD) rank among the main causes for visual impairment (VI). (Wong et al., 2014; Mitchell et al., 2018; World Health Organization, 2019) The populations of the Western world have increasingly aged in the last decades and are predicted to continue ageing in the future, which goes hand in hand with a rise of age-related diseases that already represent a large social and economic burden. (United Nations, Department of Economic and Social Affairs, 2017) In Germany, estimated prevalence of severe VI and blindness range between 200,000 to 1 million and 80,000 to 500,000, respectively, underscoring the huge impact on society and economy. (Finger, 2007; Mauschitz et al., 2019b) This growing relevance supports the urgent need for further research on pathogenesis and, subsequently, therapeutic targets which, amongst other endeavors, require the application of various robust epidemiologic approaches.

Epidemiology

Epidemiology has been defined as “the study of the distribution and determinants of disease frequency” and evaluates diseases, adjacent factors, and methods for their control. (MacMahon and Pugh, 1970; Rothman, 2012; Epidemiology is a science of high importance, 2018). Apart from “simply applying statistics”, epidemiology evaluates and considers important concepts such as ***confounding*** or ***bias*** that may influence or even hamper

conclusions from analyzed data. A confounder is a factor that influences both, the outcome and the independent variable and hence may suggest an association that is not in fact present. A classic example of confounding is the relation of higher prevalence of Down-Syndrome with a later birth order of the child. The underlying confounder in this obvious example is maternal age at birth, which increases the risk of Down-Syndrome. Yet, confounders are often less trivial to identify than in the aforementioned example. A bias describes a systematic error that cannot be eliminated by increasing sample size (as compared to a random error). Typical examples include **selection bias**, in which recruited individuals differ from "outside" individuals considering the investigated factors, or **recall bias**, that describes (unintentionally) wrong data reported by individuals. Epidemiologic approaches aim to first identify and subsequently eliminate or reduce confounding or biases. (Stark and Mantel, 1966; Rothman, 2012)

Various important and nowadays obviously explicit risk factors such as tobacco and alcohol use have been identified through epidemiologic studies. One of the first and most famous epidemiological population studies, the 'Framingham Study', was established in 1948 with the over-arching aim to investigate risk factors for coronary heart disease and atherosclerosis. Among others, the study has discovered the relation of smoking and heart attack and it has been running until today with the third generation of participants included. (DAWBER et al., 1951; Bhopal et al., 2011; Mahmood et al., 2014) Also new threats such as Shiga toxin-producing Escherichia coli or re-emerging threats such as the poliovirus are subject to epidemiologic approaches and contribute to an evolving epidemiology. (Bhopal et al., 2011)

Interestingly, the definition of epidemiology has adapted over the past decades depending on methodological and societal developments and needs and has been reported as an ascending scientific field. (Rothman, 2007a; Frérot et al., 2018) In today's era of **big data**, modern epidemiologic approaches are urgently needed to analyze and interpret large-scale amounts of data in complex diseases. (Olshan et al., 2019) The aforementioned increasing

societal impact underscores the urgent need to collect and analyze large-scale data in order to find effects that may not occur or even be masked in small studies.

In general, the type of study and source of data ought to be chosen depending on the specific research question and the investigated outcome (e.g. rare outcome, frequent outcome, biomarker identification).

Multicenter data

In case of clinical exposures, outcomes or procedures with a low prevalence in the general population, a successful collection of large datasets can be achieved by pooling data from different specialized sites. Recruitment is based on the outcome and, thus, the sample size of a rare outcome can be increased significantly enabling sufficient statistical power for meaningful calculations. It is, however, crucial to evaluate data from different sources for heterogeneity as successful pooling requires comparable data without systematic differences or bias. In recent years, the term "**real world data**" has emerged as an addition to randomized clinical trials (RCT), which are based in an "artificial" setting and usually do not represent clinical reality. Particularly, the complexity of diseases in every day clinical practice justifies another approach to support or even extend the results from "artificial" RCTs. (Rothman, 2007b)

In **Study 1** of this thesis, we collated pre- and post-surgical "real world data" for a relatively rare surgical ophthalmic procedure, the **Yokoyama procedure**. Highly myopic patients have been reported to occasionally develop a horizontal and vertical strabismus during adulthood, which can range from mild to severe restriction and can affect motility. Previous studies reported a deviation in the path of the lateral rectus muscle (LRM). (Kolling, 1993; Kaynak et al., 1994) For these patients, Yokoyama et al. established a surgical technique in which the LRM and superior rectal muscle (SRM) are joined by a suture, which particularly suitable for myopic eyes with thin a sclera. An additional medial rectus recession (MRR) in these patients has been discussed but the clinical benefit remained unclear. (Yokoyama et al., 2000;

Yamaguchi et al., 2010) Given the low overall frequency of this surgical procedure, only very few small studies have evaluated the effects of the procedure and results were based on single-center data from mainly Asian cohorts. (Yamaguchi et al., 2010; Ranka and Steele, 2015; Su et al., 2016) Against this background, we aimed to gather data from 14 clinical sites in Germany and Switzerland to create one of the globally largest “real word datasets” on the effects of the Yokoyama procedure with and without additional MMR.

Population studies

In contrast to aforementioned clinical studies, population-based studies investigate a group of individuals taken from the **general population** and display an excellent source of data for relatively frequent exposures and outcomes. Population-based studies provide a large platform for the analysis of exposure-outcome relations and typically address multiple (sets of) research questions and hypotheses. Some of which may be set a priori while others can occur within the course of the study based on advanced research or interim data analyses. (Szklo, 1998; Rothman, 2012) The advantages of large-scale population studies include among others the longitudinal perspective, the standardization of assessments, the statistical power, and the potential generalizability to the general population. Particularly, the external validity of its results is a key feature attributed to population studies. (Szklo, 1998) While most population-based studies are established for a prospective follow-up period with longitudinal data assessments, they can already answer a variety of research questions based on cross-sectional data. The latter applies e.g. to the identification of potential **biomarkers** in the general population which can subsequently be evaluated in longitudinal studies. In **Study 2** of this thesis we examine specific retinal biomarkers of brain atrophy using cross-sectional data from the population-based **Rhineland Study**.

Importantly, all assessments need to be performed systematically and standardized and hence should be reproducible independent of the person performing the assessment. In order to maximize data quality and to avoid bias, recruitment ought to be random within the

population and independent of exposure status. The same applies to the actual assessments at baseline and follow-up visits, which need to be conducted in all participants. (Szklo, 1998; Ertl et al., 2020) As compared to (small) studies which are based on a specific exposure or disease (e.g. clinical cohorts), population studies often come with large statistical power and may be able to detect smaller associations and effects that may have been overlooked otherwise. Given that recruitment is independent of exposure and outcome, results allow for external validity, i.e. the findings can be transferred to similar populations (or even the general population). (Ertl et al., 2020) **Studies 2 – 4** of this thesis are based on population study data, in particular from the **Rhineland Study** as well as from multiple studies of the **European Eye Epidemiology (E3) – consortium**.

Rhineland Study

Study 2 of this thesis is based on data from the Rhineland Study (German: Rheinland Studie; www.Rheinland-Studie.de), a community-based prospective population study with focus on normal brain ageing and development of brain pathology over time. The study is conducted by Population Health Sciences of the German Center for Neurodegenerative Diseases (DZNE). The objectives are to investigate (physiological) ageing and to identify modifiable and non-modifiable risk factors as well as biomarkers for neurodegenerative and other age-related diseases. The comprehensive and standardized deep phenotyping comprises brain magnetic resonance imaging (MRI), cognitive tests, sampling of blood (genetics and –omics), urine and stool, cardiovascular examinations, physical fitness exams and assessments of the sensory system including ophthalmic examinations. Up to 20,000 inhabitants of two geographically defined areas in the city of Bonn, Germany, who are 30 years of age or older, are scheduled to partake. The people living in those areas are predominantly German with Caucasian ethnicity and participation in the study is possible by invitation only. All inhabitants of the target areas who are at least 30 years of age will be invited to participate. The only exclusion criterion is insufficient German language skills to

give informed consent. The baseline recruitment started in March 2016 and follow-up invitations are scheduled every 3 years starting end of 2022 for a minimum period of 30 years. (Mauschitz et al., 2019a; Mauschitz, 2019)

From **2014 to 2018** I have worked as a **full-time PhD candidate** at the Rhineland Study and successfully defended my **PhD thesis in 2019**. Similar to **Study 2**, my previous work within the Rhineland Study included research on **retinal biomarkers** using spectral-domain optical coherence tomography (SD-OCT) in the general population. (Mauschitz et al., 2019a; Ward et al., 2020)

European Eye Epidemiology (E3) consortium

Studies 3 and 4 of this thesis are based on an international collaboration within the E3-consortium (https://www.eye-epi.eu). The E3-consortium is a collaborative network across Europe with the overarching aim of developing and analyzing large datasets to increase understanding of eye diseases and vision. (Delcourt et al., 2016) As of today, the E3 consortium is a cooperation between 31 groups originating from 14 different European countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Lithuania, the Netherlands, Norway, Portugal, Switzerland, United Kingdom) and comprises both population-based and other studies (case-control, cases only, randomized trials), providing ophthalmological data on approximately 170,000 European participants. E3 brings together experts on eye diseases from various disciplines such as clinicians, epidemiologists, statisticians, and computer scientists in order to

1. promote and sustain collaboration and sharing of knowledge in the field of ophthalmic epidemiology in Europe
2. lay particular focus on
    a. the harmonization of methods for future research
    b. the estimation and projection of frequency and impact of visual outcomes in European populations

    c. temporal trends and European sub-regions
3. to identify risk factors and pathways for eye diseases (lifestyle, vascular and metabolic factors, genetics, epigenetics and biomarkers)
4. to develop and validate prediction models for eye diseases
5. to educate and develop the next generation of ophthalmic epidemiologists

Among other topics, previous work in the context of E3 include epidemiological research on frequent ophthalmic diseases such as **AMD** (Colijn et al., 2017; Colijn et al., 2019) as well as the use of **retinal imaging biomarkers** using SD-OCT. (Mauschitz et al., 2018)

Retinal biomarkers and neurodegeneration

The neurosensory retina and the brain derive from the same neural tissue, share morphologic and physiologic similarities and maintain direct synaptic connections over the whole life span. (Chang et al., 2014; Mauschitz, 2019) Similar to the aforementioned rise in age-related ophthalmic diseases, prevalence and incidence of neurodegenerative diseases such as Alzheimer's disease (AD) is severely increasing due to demographic changes. (Patterson, 2018; Grande et al., 2020)

Nowadays, retinal layer measurements using high-resolution SD-OCT have been discussed as potential biomarkers for a variety of neurological and neurodegenerative diseases including multiple sclerosis (MS) and dementia. (Jones-Odeh and Hammond, 2015; Britze and Frederiksen, 2018; Mutlu et al., 2018a) Retinal imaging is non-invasive, easily assessable and cost-efficient and, therefore, potentially suitable for mass screening. Modern segmentation algorithms enable the automated and precise identification of all retinal layers including the outer retina (**Figure 1**).

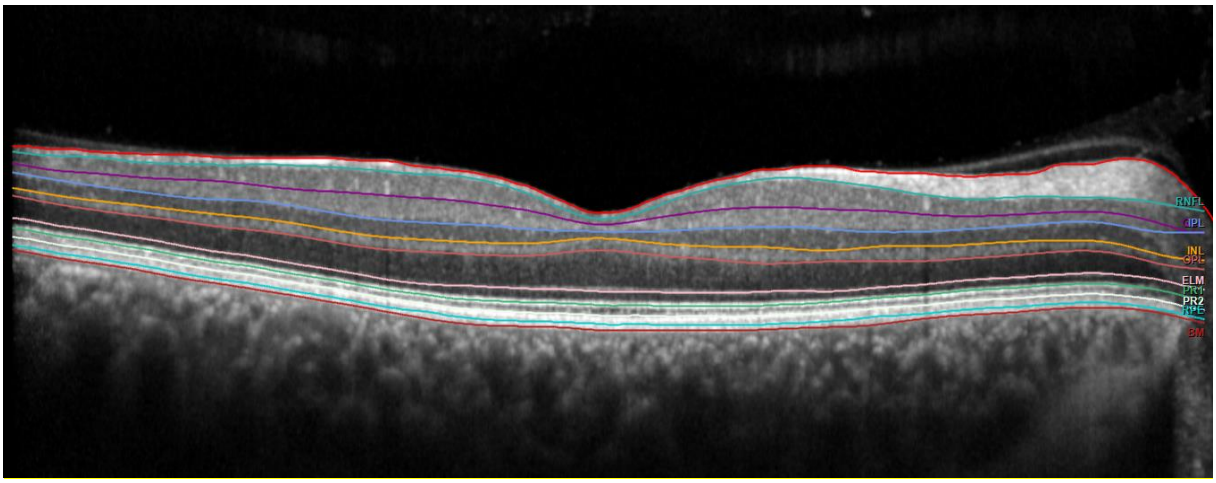

Figure 1. Automated segmentation of retinal layers based on retinal SD-OCT imaging (Source: M. M. Mauschitz, Department of Ophthalmology, University of Bonn)

Previous studies on the relation of SD-OCT-based retinal measurements and magnetic resonance imaging (MRI)-assessed brain parameters, however, were mainly based on small samples of mostly cognitively impaired participants. (Ong et al., 2015; Casaletto et al., 2017) and no large-scale data exist on the relation in the general population. Against this background, in **Study 2** we evaluated associations of various retinal layers with cerebral structural measures and hence their usability as biomarker using data from the Rhineland Study.

Age-related macular degeneration

As mentioned above, AMD is a highly frequent cause of severe VI and blindness in all high-income countries affecting up to 25% of the population above the age of 55 and given demographic trends, AMD prevalence is projected to increase by 15% and incidence by 75% until 2050.(Finger et al., 2011; Klein and Klein, 2013; Mitchell et al., 2018; Li et al., 2020; Mauschitz et al., 2022) Late-stage AMD has a significant impact on the quality of life and the economic impact has been estimated to be €89.5 billion in the European Union. (Brown et al., 2005; Jaki Mekjavić et al., 2019)

While several classification systems exist for AMD, the disease can clinically be divided into an early, an intermediate and two late stages (Ferris et al., 2013). Differences exist between common classification systems, but early AMD is usually characterized by the presence of small or intermediate drusen in the retina. Drusen (**Figure 2**) are accumulations of metabolic by-products such as oxidated debris of lipids and proteins under the retinal pigment epithelium (RPE) and represent a hallmark lesion of AMD. (Curcio et al., 2005; Jarrett and Boulton, 2012; Mitchell et al., 2018) While some patients experience mild symptoms, early AMD often remains asymptomatic. The occurrence of intermediate and large drusen and/or pigmentary changes define the stadium of intermediate AMD (iAMD), in which patients may notice symptoms such as difficulties under challenging light conditions (low luminance and/or low contrast), metamorphopsia and which has a high risk of conversion to late stage disease manifestations. (Ferris et al., 2013; Mitchell et al., 2018)

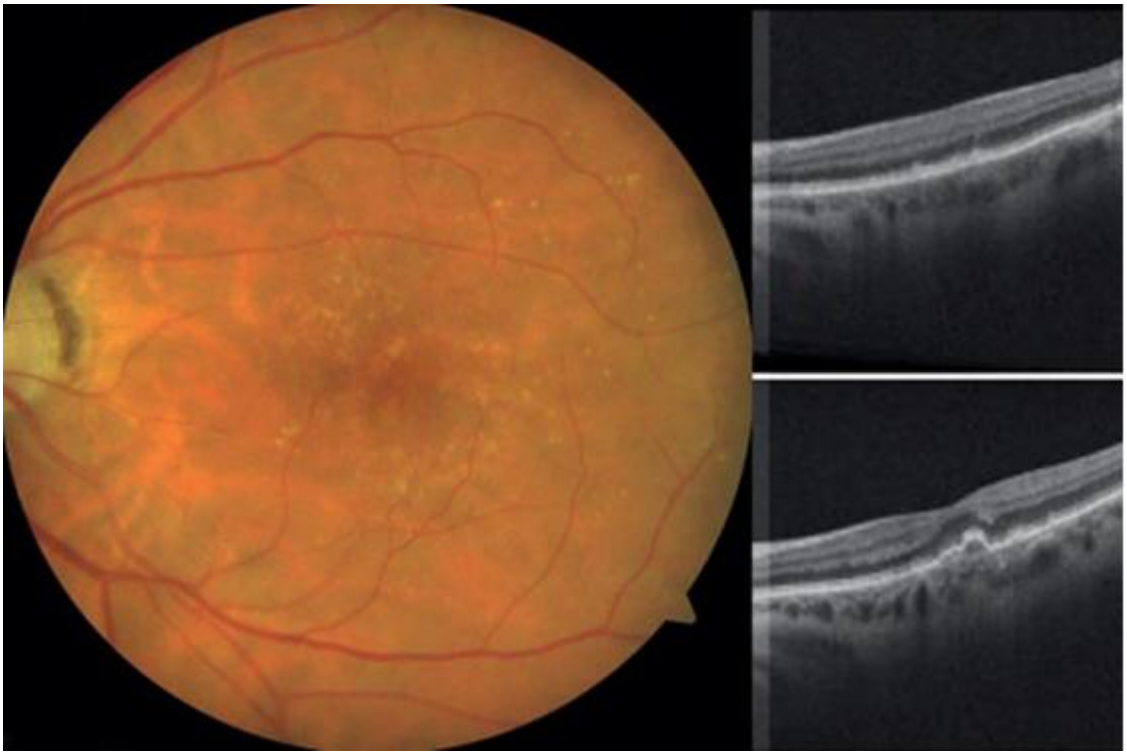

Figure 2. (adapted from (Mitchell et al., 2018)). Drusen as yellowish lesions on color fundus photography (left) and as elevations of the retinal pigment epithelium on SD-OCT (right).

Late stage AMD is traditionally distinguished into an exudative neovascular (“wet”) and a non-exudative (“dry”) stage. Neovascular AMD is characterized by the proliferation of choroidal neovascularisations (CNV), which can lead to retinal edema, hemorrhages, RPE detachments, exudates, and subsequently to fibrous scar tissue (**Figure 3**). In contrast, non-exudative late AMD is characterized by atrophy of the outer retina, so-called geographic atrophy (**Figure 4**). There is no exclusive dichotomy between the two diseases states, both may develop in the same eye. (Ferris et al., 2013; Mitchell et al., 2018)

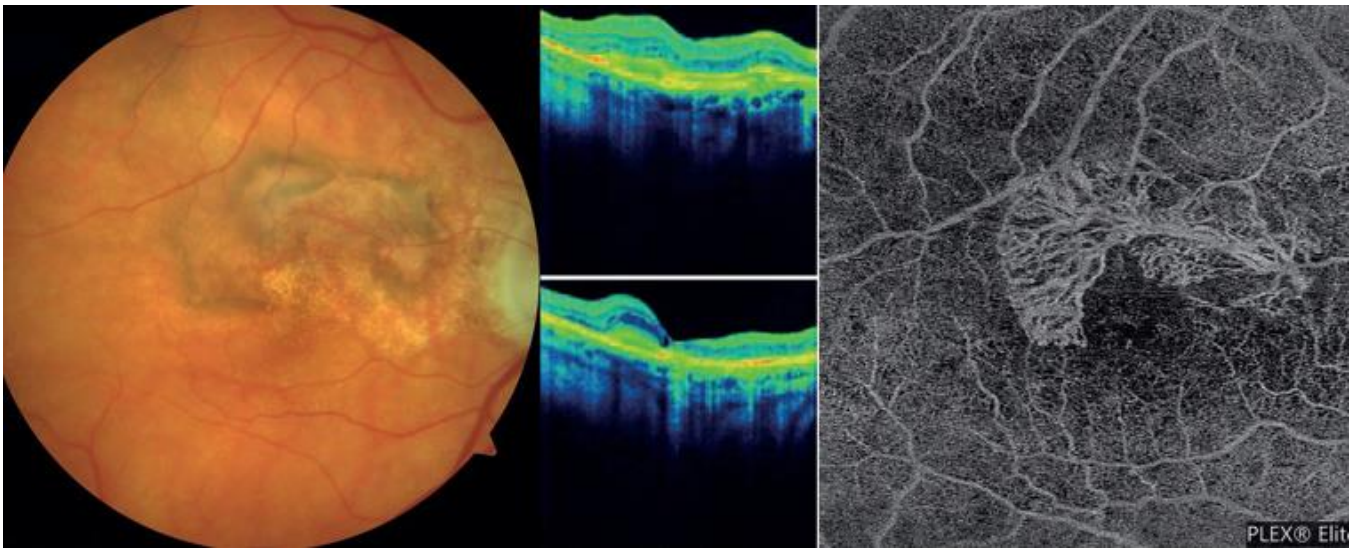

Figure 3. (adapted from (Mitchell et al., 2018)). Neovascular AMD on color fundus photography ,SD-OCT, and OCT-angiography.

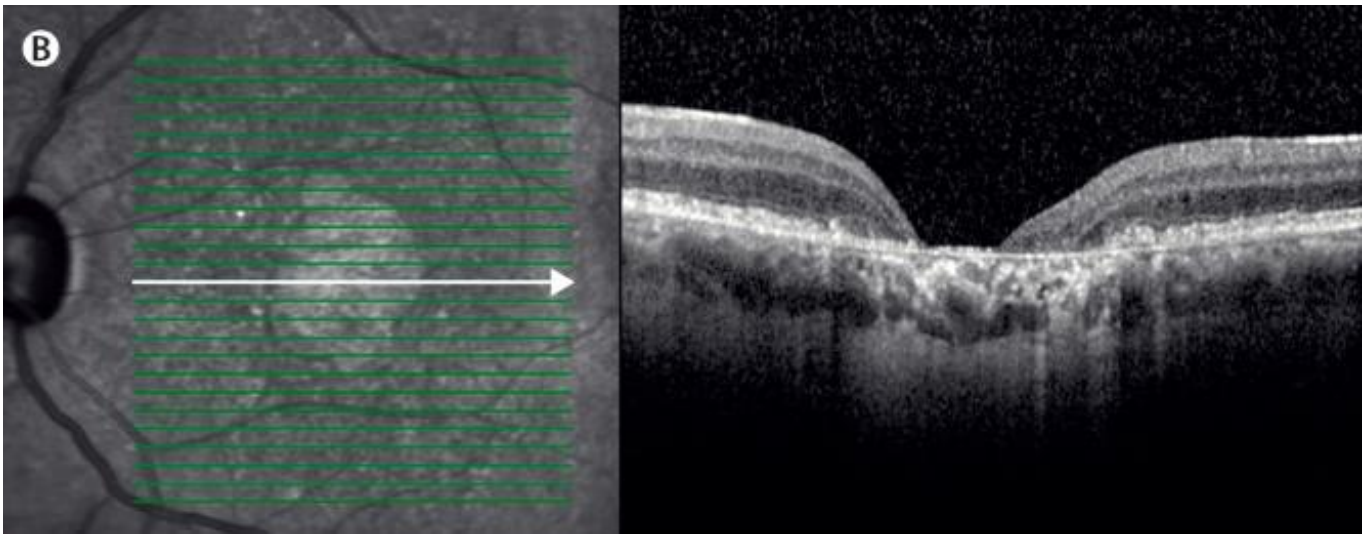

Figure 4. (adapted from (Mitchell et al., 2018)). Geographic atrophy on near-infrared (NIR) – imaging and SD-OCT.

AMD is a complex disease with genetic and environmental risk factors associated with ageing. Despite the identification of various risk genes and several decades of research into AMD, we still have no specific evidence-based therapeutic intervention to prevent AMD onset or delay progression to late stage. Hence, identification, management and prevention of lifestyle risk factors remain crucial. (McGuinness et al., 2017b; Colijn et al., 2019; Colijn et al., 2021; Mauschitz et al., 2022) Apart from age, smoking has been reported to increase AMD risk 2-4-fold (Heesterbeek et al., 2020), while adhering to a Mediterranean diet (MeDi) was reported to reduce the risk of late AMD. (Merle et al., 2019)

Other lifestyle factors such as **physical activity** (PA) have previously been discussed beneficial, but studies were mainly small to moderately sized, based on cross-sectional data only and reported conflicting results. (Knudtson et al., 2006; Klein et al., 2010; Mares et al., 2011; Munch et al., 2013; Gopinath et al., 2014; Loprinzi et al., 2015; McGuinness et al., 2016; McGuinness et al., 2017a) Against this background, we collated and meta-analyzed longitudinal data from several population-based cohort studies of E3 to better characterize the impact of PA on AMD onset and progression in **Study 3**.

Apart from lifestyle risk factors, chronic inflammation and increased oxidative stress have been discussed as patho-etiogenetic drivers of AMD. (Jarrett and Boulton, 2012; Colijn et al., 2017; Choudhary and Malek, 2019; Heesterbeek et al., 2020; Spaide et al., 2020) The retina is a metabolically highly active tissue with a large turnover of lipids and proteins and several metabolites have been associated with AMD occurrence and formation of retinal lesions such as drusen. Previous studies suggested an association of specific lipoproteins such as the high density lipoprotein (HDL) with larger prevalence of AMD.(Colijn et al., 2019; Kersten et al., 2019) Interestingly, there is strong evidence for common pathways between AMD and systemic diseases such as cardiovascular disease (CVD), which are both age-related multifactorial diseases and share various aforementioned risk factors. (Schnabolk, 2019; Mauschitz and Finger, 2022)

Previous studies investigated the relation of AMD and specific **systemic medications**, which interfere with pathways that also play a role in AMD pathogenesis and hence may affect it. These drugs include lipid-lowering drugs (LLD) for the lipid metabolism, which are commonly prescribed in CVD (Francula-Zaninovic and Nola, 2018; Roizenblatt et al., 2018) as well as anti-diabetic drugs (particularly metformin), which have been hypothesized to reduce general inflammation and oxidative stress. (Stewart et al., 2020; Blitzer et al., 2021) Results of these studies, however, have been inconsistent, based on small sample size or used self-reported AMD as outcome. (Klein et al., 2003; Guymer et al., 2013; VanderBeek et al., 2013; Le Ma et al., 2015; Roizenblatt et al., 2018) Metformin and LLD rank among the top prescribed drugs in Germany and Europe, underscoring the potential impact and relevance on public health issues. (Fuentes et al., 2018; Schwabe and Ludwig, 2020) In **Study 4** we explored associations between the use of several systemic medications and presence of AMD in the general population using data from several E3 studies.

Results

Wabbels B, Fricke J, Schittkowski M, Gräf M, Lorenz B, Bau V, Nentwich MM, Atili A, Eckstein A, Sturm V, Beisse C, Sterker I, Neppert B, **Mauschitz MM**. **Yokoyama procedure for esotropia associated with high myopia: real-world data from a large-scale multicentre analysis.** Acta Ophthalmol. 2021 Dec;99(8):e1340-e1347. DOI: 10.1111/aos.14808

As secondary complication, high myopic patients may develop strabismus due to globe dislocation out of the normal extraocular muscle cone. Surgical correction of this strabismus type is possible by joining the superior and lateral rectus muscle without the need for a scleral suture called Yokoyama procedure. Thus far, data from large patient samples on the Yokoyama procedure as well as on a potential effect of an additional medial rectus recession (MRR) have been lacking. Therefore, we pooled retrospective patient data of 14 clinical sites in Germany and Switzerland and analyzed postoperative results and respective determinants using multivariable regression models. We included 133 patients with a mean age of 59.7 ± 13.4 years and a previous surgery between 2008 and 2017. In these patients, mean preoperative esotropia (both, Yokoyama with or without MRR) was 23.8° ± 4.6° and angle of preoperative esotropia increased with age. The postoperative esotropia was 8.7° ± 9.9° with 6 patients being overcorrected. While preoperative esotropia was highly associated with postoperative results, we found no association of additional MRR with any of our postoperative outcomes. The Yokoyama procedure had a higher absolute effect in patients with higher preoperative esotropia.

Our study confirms the positive effect of the Yokoyama procedure on strabismus due to high myopia in one of the largest “real world datasets”. In some cases, MRR may be needed due to muscle contracture, although additional MRR did not affect our postoperative outcomes. In patients with bilateral high myopic strabismus, correction of both eyes seems beneficial. The effect size of the Yokoyama procedure appears to be mainly driven by preoperative esotropia.

Check for updates

Acta Ophthalmologica

Acta Ophthalmologica 2021

Yokoyama procedure for esotropia associated with high myopia: real-world data from a large-scale multicentre analysis

Bettina Wabbels,[1] Julia Fricke,[2] Michael Schittkowski,[3] Michael Gräf,[4] Birgit Lorenz,[1,4] Viktoria Bau,[5] Martin M. Nentwich,[6] Abed Atili,[7] Anja Eckstein,[8] Veit Sturm,[9,10] Christina Beisse,[11] Ina Sterker,[12] Birte Neppert[13] and Matthias M. Mauschitz[1]

[1]Department of Ophthalmology, University of Bonn, Bonn, Germany
[2]Department of Ophthalmology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany
[3]Department of Ophthalmology, Section for Strabismus and Neuroophthalmology, University Medicine Goettingen, Goettingen, Germany
[4]Department of Ophthalmology, Justus-Liebig University Giessen and Universitaetsklinikum Giessen and Marburg GmbH Campus Giessen, Giessen, Germany
[5]Medical practice for ophthalmology, Department of Ophthalmology, Eye Clinic Dresden Friedrichstadt, Dresden, Germany
[6]Department of Ophthalmology, Julius-Maximilians University Würzburg, Würzburg, Germany
[7]Department Strabism and Oculoplastic, Eye-Clinic-Esslingen, Esslingen, Germany
[8]Department of ophthalmology, University Duisburg Essen, Essen, Germany
[9]Department of Ophthalmology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland
[10]University of Zurich, Zurich, Switzerland
[11]Department of Ophthalmology, University of Heidelberg, Heidelberg, Germany
[12]Department of Ophthalmology, University of Leipzig, Leipzig, Germany
[13]Department of Ophthalmology, University of Luebeck, Luebeck, Germany

ABSTRACT.

Purpose: **High myopic patients may develop strabismus due to globe dislocation out of the normal extraocular muscle cone. Surgical correction of this strabismus type is possible by joining the superior and lateral rectus muscles without the need for a scleral suture called the Yokoyama procedure. Data from large patient samples and the evaluation of a potential effect of an additional medial rectus recession (MRR) have been lacking so far.**

Methods: **We pooled retrospective patient data of 14 departments of ophthalmology in Germany and Switzerland and analysed determinants of postoperative results using multivariable regression models.**

Results: **We included 133 patients (mean age: 59.7 ± 13.4 years, surgery between 2008 and 2017) with a mean preoperative esotropia (both Yokoyama with and without MRR) of 23.8°±4.6°. The angle of preoperative esotropia increased with age. The postoperative esotropia was 8.7° ± 9.9°, and six patients were overcorrected. While preoperative esotropia was highly associated with postoperative results, we found no association of additional MRR with any of our postoperative outcome measures. The Yokoyama procedure had a higher absolute effect in patients with higher preoperative esotropia.**

Conclusion: **Our study confirms the positive effect of the Yokoyama procedure on strabismus due to high myopia in large-scale real-world data. In some cases, MRR may be needed because of muscle contracture, although additional MRR statistically did not affect the postoperative outcome. In patients with bilateral high myopic strabismus, correction of both eyes seems beneficial. The effect size of the Yokoyama procedure appears to be mainly driven by preoperative esotropia.**

Key words: esohypotropia – heavy eye – high myopia – muscle dislocation – strabismus fixus

Acta Ophthalmol. 2021: 99: e1340–e1347

© 2021 The Authors. Acta Ophthalmologica published by John Wiley & Sons Ltd on behalf of Acta Ophthalmologica Scandinavica Foundation.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

doi: 10.1111/aos.14808

Introduction

High myopic patients have previously been reported to occasionally develop a horizontal and vertical strabismus during adulthood, mostly after the third decade of life. In these patients, axial length (AL) of the globe is usually more than 26.5 mm and motility can be reduced. The phenotypical appearance ranges from small-angle esotropia with mild abduction deficit to strabismus fixus with severe restriction (Kaynak et al. 1994; Sturm et al., 2008). In the majority of cases, the (more) myopic eye is hypotropic and turned inwardly. Exotropia is less frequent.

Kolling demonstrated the path of the lateral rectus muscle (LR) to be oblique from its insertion dorsally downwards using both in situ imaging and CT and MRI scans showing the nasal displacement of the vertical rectus muscles and, particularly, inferonasal displacement of the LR (Kolling 1993). The decisive innovation

introduced by Herzau was to normalize the pulling direction of the slipped LR by adding a retroequatorial myopexy of this muscle to the conventional recess and resect surgery (Herzau & Ioannakis 1996). Krzizok by MRI demonstrated that the path of the LR could be normalized by this procedure (Krzizok et al. 1997), which generated various case reports on this technique and modifications (Hayashi et al., 1999; Aoki et al., 2003; Rowe & Noonan 2006; Sturm et al., 2008).

Yokoyama et al. elaborated the fundamental idea by joining the lateral and superior rectus muscles by a muscle suture 15 mm behind the insertion (anterior to their pulleys, anterior muscle belly union, MBU). Avoiding the scleral suture is an advantage, especially for high myopic eyes with scleral thinning. In addition, the technique is preferable for surgeons who rarely perform myopexy (Yokoyama et al. 2000; Yamaguchi et al. 2010). Yamaguchi and colleagues showed by MRI the superotemporal shift of the posterior part of the globe out of the normal extraocular muscle cone and demonstrated that MBU of the superior rectus and LR restored their normal anatomic relationship (Yamaguchi et al. 2010). However additional medial rectus recession (MRR) was performed in 80% of the eyes (Yamaguchi et al. 2010). Due to further reports on these modifications (Yamada et al., 2002; Godeiro et al., 2009), LR myopexy lost popularity over time. Ranka and Steele summarized in their review: 'The Faden-OP (LR) showed good postoperative results, but this procedure is technically difficult, particularly in high myopes with thin sclera, whereas the Yokoyama procedure eliminates the risk of sclera perforation and minimizes the risk of anterior segment ischemia' (Ranka & Steele 2015).

So far, only smaller studies of patients with the Yokoyama procedure (≤25 patients) have been published (overview in Su et al. 2016). The aim of this study was to evaluate the effect of the Yokoyama procedure alone or combined with MRR in a large multicentre cohort for different subsets of patients.

Methods

Data acquisition

All university hospitals in Germany and two non-university hospitals with large orthoptic departments were approached as to previously performed Yokoyama surgeries, and whether they would like to participate in the study. We finally included data from 14 sites: university hospitals of Bonn, Dresden, Essen, Frankfurt, Giessen, Göttingen, Heidelberg, Köln, Leipzig, Lübeck, Rostock, Würzburg, hospitals of Esslingen, Germany, and St. Gallen, Switzerland. Patient data sets ranged from 2 to 23 patients per site who underwent surgery between 2008 and 2017. These included anamnestic data and preoperative and postoperative findings, that is horizontal and vertical angles of strabismus (measured with the alternating prism and cover test in 0.3m, if visual acuity was poor, with the Krimsky test), AL, eye motility, head position, further ocular disorders, details concerning Yokoyama surgery and potentially further surgeries. The Yokoyama procedure was defined as joining the superior rectus and LR muscles by an intermuscular suture. The performance of additional procedures such as MRR and the choice of the suture material was decided upon by the individual different departments. All amounts given for an optional MRR are given for the actual surgery. When both eyes were operated simultaneously or within a timeframe of four weeks, the given postoperative results are those for bilateral surgery.

Data analyses

The study was approved by the local institutional board of the University of Bonn. Data were pseudonymized and conveyed via Excel (Microsoft Excel 2010; Microsoft, Redmond, WA, USA) sheets to the Dept. of Ophthalmology of the University of Bonn.

Whenever angles of strabismus were provided in PD (Δ, pdpt, cm/m), they were converted in degree (°, deg) with the formula $angle/deg = tan^{-1}0.01\Delta$ (Basiakos et al., 2019). Due to the nonlinearity of the tangens function, the prism dioptre unit (cm/m) is not appropriate for statistical calculations.

Horizontal angles for esotropia are indicated with positive values, whereas negative values represent exotropia. Concerning values for the vertical deviation, in unilateral cases the given values indicate the amount of hypotropia of the affected eye, and in bilateral cases, the difference between the eyes.

Different groups (e.g. with and without MRR, with and without previous surgery) were compared using Student's *t*-test, Wilcoxon's test and the chi-square-test depending on data distribution.

In order to evaluate surgical effects, we defined four postoperative outcomes (for horizontal and vertical angles, respectively): the absolute postoperative angle, the absolute difference between pre- and postoperative angle, the relative difference between pre- and postoperative angle (defined as absolute difference divided by preoperative angle; only possible in horizontal angles, since vertical angles were zero for many patients) and whether the absolute postoperative angle was ≤ 5° (binary variable). Subsequently, we analysed determinants of the first three outcomes using multivariable regression modelling and for the binary outcome using Cox regression modelling. All models were adjusted for age, sex, AL, MRR, previous strabismus surgery, additional surgery, laterality (uni- vs. bilateral) and preoperative angle. The latter was not corrected in the analysis of relative difference, as it is part of the outcome. Moreover, we performed additional sensitivity analyses adjusting for different sites.

Analyses were performed using SPSS 25 (IBM Inc., Armonk, New York) and RStudio (R version 3.4.1; RStudio, Inc., Boston, MA; available in the public domain at https://www.rstudio.com/). A significance level was set to $p = 0.05$ for the group analyses and corrected for multiple testing for the regression analysis using the Bonferroni correction ($p = 0.05/8 = 0.00625$).

Results

We received data of 140 patients. Seven patients who had undergone atypical Yokoyama procedure joining other muscles than the LR and superior rectus were excluded. Of the included 133 patients, 100 (75%) were female. The mean age was 59.7 years (see Table 1), and 109 patients (82%) were ≥ 50 years of age.

About 37 patients (28%) had undergone prior eye muscle surgery. Of the 20 patients where we had details, 12 had combined convergence surgery (recess–resect) on the operated eye, 3 had surgery on the other eye and the remaining five had other surgeries.

Sixty two patients (47%) were pseudophakic; therefore, refraction was not analysed. Data on AL of the operated eye(s) were available in 109 patients (82%), AL of the fellow eye in 86 of the 124 patients with unilateral surgery, as some centres did not provide AL in (all of) their patients.

AL was ≥ 28 mm in all patients except two, who had typical reduced motility and were therefore included in the study. Patient characteristics and details are summarized in Table 1.

Patient characteristics and pre- and postoperative findings (133 patients, 124 unilateral surgery and 9 bilateral).

The preoperative angle of esotropia was associated with age, even when corrected for sex and AL, which themselves were not associated, respectively. Hence, with every year of increasing age, the esodeviation was 0.22° higher (95% confidence interval (CI): 0.01–0.44; p = 0.0385). There was no significant association of the vertical angles with age, sex or AL.

Six patients had preoperative esotropia of ≤ 5° (vertical angles 5.0–19.3°), and none of them had prior surgery for strabismus. Four of them had typically reduced eye motility, and AL ranged from 28.3 to 37.2 mm.

Surgery

Surgery was performed on the right eye in 69 patients, on the left eye in 55 patients and on both eyes in nine patients. Figure 1 displays an overview.

The suture material used for the Yokoyama procedure was non-resorbable in 125 patients (83 polyethylene terephthalate (Mersilene®; Ethicon, Somerville, USA), 24 polyester, 13 polyamide, 4 silk, 1 polypropylene), mostly 4-0 or 5-0, and resorbable (polyglactin/PGA) in 8 patients.

We found no differences between patients with and without prior strabismus surgery concerning sex, age, AL, preoperative angles of strabismus (horizontal and vertical) or suture material. More patients without than with prior strabismus surgery were pseudophakic (54% vs. 27%). Patients with bilateral surgery showed a tendency (p = 0.06) to have higher preoperative esotropia than patients with unilateral surgery [mean 35.7° ± 20.3° (median 25.0°) versus mean 23.0° ± 13.8° SD (median 19.3°), respectively].

In patients with unilateral surgery, AL was ≥ 28 mm in the fellow eye in 43/86 patients (50%) and ≥ 30 mm in 32/86 patients (37%).

Preoperative esotropia was larger in patients with MRR compared to those without MRR (32.6° ± 13.4 SD vs. 20.3° ± 13.6 SD; p < 0.00001). Moreover, patients with MRR were older, which was likely confounded by an increase in esotropia with age (see Table 2).

The choice to perform additional MRR (2.5 to 12 mm) was only dependent on the decision of the individual surgeons. In about half of the patients with additional MRR, the surgeons had decided this before surgery due to large horizontal angles. In the other half, MRR was performed because it was intraoperatively difficult to join the lateral und superior rectus muscle due to MR contracture.

There were no significant differences concerning sex or suture material, but we found a tendency to higher AL in the group with only Yokoyama surgery.

Table 1. Patient characteristics and pre- and postoperative findings (133 patients, 124 unilateral surgery and 9 bilateral)

	n	Mean ± SD	Median	Range	
Age (years)	133	59.7 ± 13.4	60.1	16	87
Axial length (AL) (mm)	109	32.3 ± 2.6	32.4	26.4	37.5
Preoperative esotropia (°)	133	23.8 ± 14.6	21.8	0	70.0
Postoperative horizontal angle (°)	133	8.7 ± 9.9	5.0	−11.5	35.0
Absolute effect (°) (horizontal)	133	15.2 ± 10.6	13.8	−2.3	50.0
Preoperative hypotropia (°)	133	8.0 ± 5.3	6.8	0	26.6
Postoperative vertical deviation (°)	133	2.8 ± 4.1	0	0	16.7
Absolute effect (°) (vertical)	133	5.2 ± 5.4	5.7	−9.1	20.0
	Preoperative			**Postoperative**	
Restricted ocular motility (abduction ≤ 15° and/or elevation ≤ 10°)	84/122	69%		38/100	38%
Abduction ≤ 15°	76/122	62%		38/100	38%
Elevation ≤ 10°	59/122	48%		33/100	33%
Relevant head turn ≥ 10°	22/129	17%		6/125	4%

Postoperative findings

Postoperative evaluation was aimed to include a follow-up of at least one month, but 29 patients did not show up for long-term follow-up or lived abroad, causing a shorter follow-up time. Follow-up ranged from 1 to 1260 days (median: 99 days, mean: 157 ± 225 days), and 92 patients had a follow-up time ≥ 8 weeks (see below). No surgical complications such as intraocular pressure rise, perforation or anterior segment ischaemia were reported. Postoperative findings are presented in Table 1.

The postoperative horizontal angle was strongly associated with the preoperative horizontal angle (see Fig. 2). For each degree of preoperative esotropia, we found a larger postoperative angle of 0.50° (95% CI: 0.39–0.56; p < 0.00001). Patients with unilateral surgery tended to have more residual postoperative esotropia as compared to patients with bilateral surgery (7.09°, 95% CI: 1.36–12.83, p = 0.02), while overall women showed a tendency to smaller postoperative angles (−3.24°; 95% CI: −6.55–0.06; p = 0.05), even with correction for AL. Both associations were not statistically significant after the Bonferroni correction.

There was no association of the postoperative horizontal angle with age, AL, prior surgery, MRR or additional surgeries.

The postoperative vertical angle (see Fig. 3) was strongly associated with the preoperative vertical angle (0.33°; 95% CI: 0.18–0.47; p < 0.0001), but not with age, sex, AL, laterality or prior strabismus surgery. Additional surgery showed a tendency to larger postoperative angles (95% CI: 0.71–5.57; p = 0.011).

We found comparable results for the absolute differences: for each degree of preoperative horizontal angle, the absolute difference between the pre- and postoperative angles increased by 0.50° (95% CI: 0.4–0.61; p < 0.00001). While women tended to have larger absolute differences (3.24°; 95% CI: −0.06 to 6.55; p = 0.05), unilateral surgery showed a tendency to be associated with smaller absolute differences between pre- and postoperative angles (−7.09°; 95% CI: −12.83 −1.36;

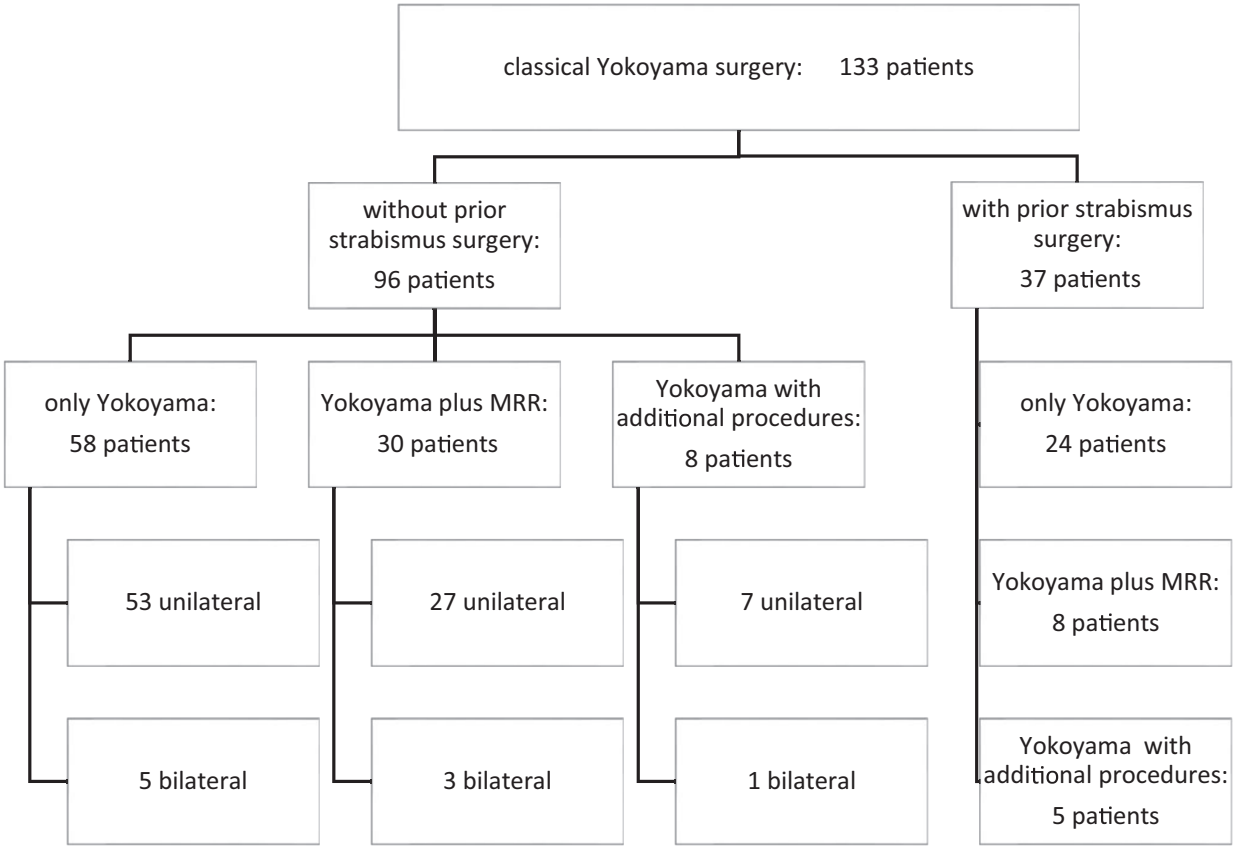

Fig. 1. Distribution of the 133 patients with classical Yokoyama procedure concerning prior strabismus surgery and additional medial rectus recession (MRR) or further procedures (plication of the lateral rectus (LR), plication of the LR and superior rectus muscle, revision of the LR, contralateral MRR). All patients with prior strabismus surgery had unilateral Yokoyama procedure.

Table 2. Comparison between pre- and postoperative data for patients with and without additional medial rectus recession (MRR)

	Without medial rectus recession					With medial rectus recession					p
	n	Mean ± SD	Median	Min	Max	*n*	Mean ± SD	Median	Min	Max	
Age (years)	95	58.07 13.74	58.60	16.20	86.60	38	63.84 11.80	63.05	20.80	83.40	0.02*
Axial length (AL) (mm)	75	32.66 2.48	32.78	27.00	37.50	34	31.38 2.56	31.29	26.43	35.90	0.02*
Preoperative esotropia (°)	95	20.33 13.57	16.70	0	70	38	32.61 13.37	33.51	9.00	60.00	P < 0.001**
Postoperative horizontal angle (°)	95	7.53 9.51	4.57	−11.50	30.96	38	11.56 10.24	9.55	−5.00	34.99	0.04*
Absolute effect (°) (horizontal)	95	12.80 9.53	11.31	−2.29	47.71	38	21.05 10.87	19.92	5.39	50.00	P < 0.001**
Preoperative hypotropia (°)	95	7.87 5.20	6.84	0	21.80	38	8.21 5.47	9.05	0	26.57	0.64
Postoperative vertical deviation (°)	95	2.46 3.66	0	0	16.70	38	3.54 4.88	0.29	0	16.70	0.44
Absolute effect (°) (vertical)	95	5.41 5.42	5.71	−8.35	20.00	38	4.67 5.34	5.66	−9.09	15.00	0.47

p = 0.02). Patients with MRR showed larger absolute differences, which is in accordance with the higher preoperative esotropia and showed no effect in the multivariable analysis (see Table 2). For the vertical deviation, the preoperative angle was the strongest determinant as well, while additional surgery showed a tendency to cause smaller differences.

We found no influence of age, sex, AL, prior surgery, MRR or additional

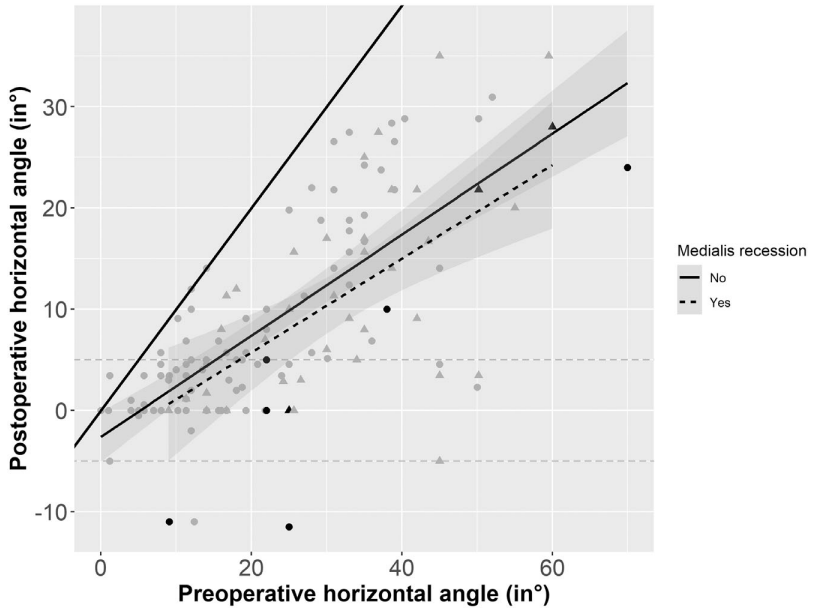

Fig. 2. Scatterplot of pre- and postoperative horizontal angles [in degree] of 133 patients, with regression lines and 95% confidence intervals. ● Patients with the Yokoyama procedure only (n = 95, grey = unilateral, black = bilateral). ▲ Patients with additional MRR (2.5 to 12.0 mm, mean 5.5 ± 3.5 mm, median 6.0 mm) (n = 38, grey = unilateral black = bilateral). Dark line = linear slope (indicates no change). Grey dotted lines = target angle (−5° to 5°).

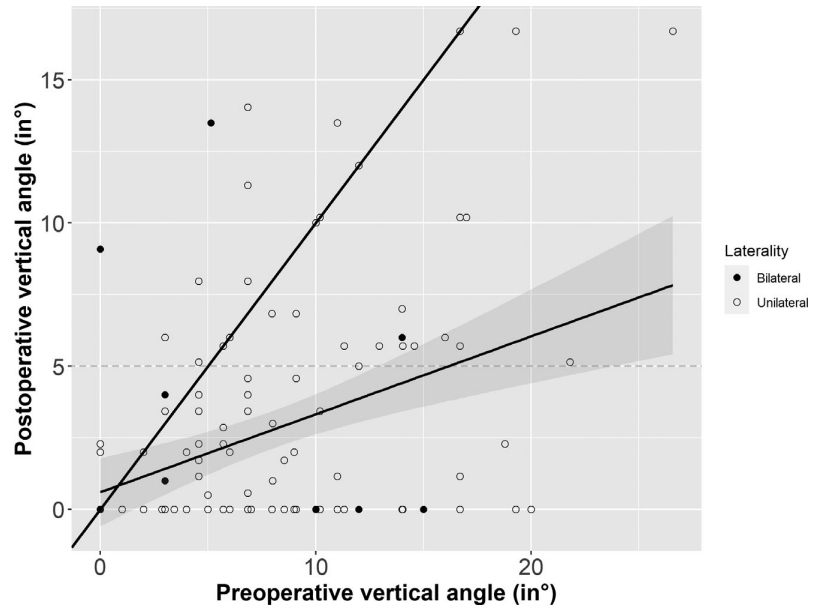

Fig. 3. Scatterplot of pre- and postoperative vertical angles [in degree] of 133 patients, with regression lines and 95% confidence intervals. grey = unilateral surgery, black = bilateral. Dark line = linear slope (indicates no change). Grey dotted line = target angle (≤5°).

surgeries on the relative difference. There was a tendency (p = 0.02) towards a higher relative effect of the surgery in patients with bilateral surgery compared to those with unilateral surgery, which did not reach statistical significance.

In our cohort, 48 % of patients showed a postoperative horizontal angle between −5° and 5°.

Larger preoperative esotropia was associated with a smaller odds ratio for an absolute postoperative horizontal angle ≤ 5° (OR: 0.89; 95% CI: 0.85–0.94; p < 0.0001; Fig. 4), while no other factor appeared to be associated.

For all postoperative outcomes, we performed sensitivity analyses adjusting for treatment site and did not find any relevant effect. In an additional sensitivity analysis, we excluded patients with a follow-up shorter than 8 weeks (56 days) and recalculated our models with the remaining 92 patients. The preoperative angle remained by far the strongest determinant and showed comparable effect sizes, while other non-significant trends vanished. Hence, the short follow-up time in some patients did not relevantly change our results.

Of the six patients with preoperative esotropia of ≤ 5°, one patient had a postoperative exotropia of −5°, the others had a postoperative esotropia between 0 and 3.4° (median: 0.5°), and vertical angles ranged from 0 to 16.4° (median: 1°). Motility was improved in all patients who had significantly reduced motility before the surgery.

Postoperative exotropia between 2° and 11.5° occurred in further five patients with preoperative esotropia between 9 and 45°. Two of these had MRR during their combined surgery before the actual procedure, in one patient the actual MRR was 10 mm (for an initial esotropia of 9°). Two of the patients had bilateral surgery with bilateral high myopia. Concerning the surgical effect on the vertical angle, in three patients the postoperative vertical angle was substantially larger than the preoperative, two of these with bilateral surgery. One patient had a postoperative exotropia and higher vertical deviation, in this patient additional myopexia of the lateral rectus muscle to the sclera had been performed.

In 26 patients, further strabismus surgery was performed (Eight combined recess–resect surgery other eye, six additional MRR, three revisions of Yokoyama surgery, two Yokoyama surgery other eye and seven other procedures). In another eight patients, further strabismus surgery was planned or discussed with the patient.

Discussion

Our study provides large-scale results of the Yokoyama procedure for

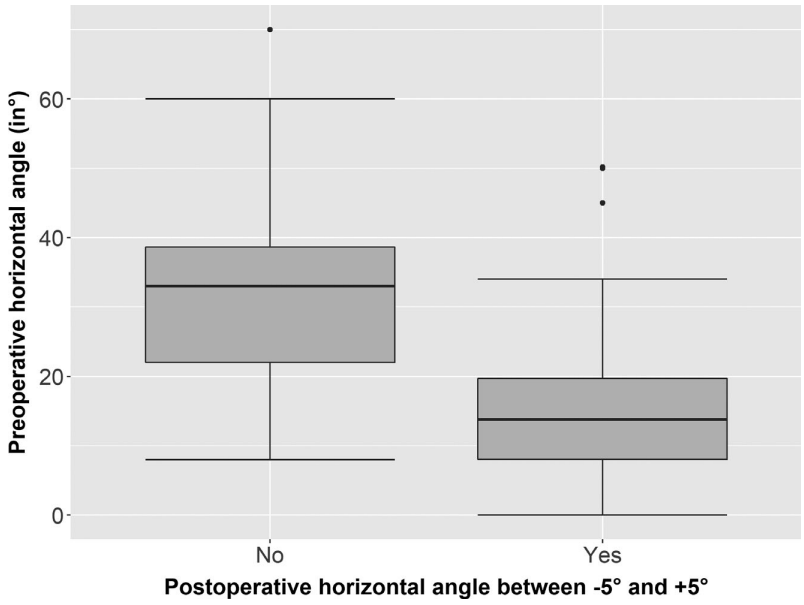

Fig. 4. Boxplot of preoperative esotropia and postoperative target angle (absolute horizontal deviation ≤ 5°).

correcting esohypotropia in patients with high myopia using data from 14 centres.

Most of our patients were 50 years or older, and magnitude of preoperative esotropia increased with age. We found the effect of the Yokoyama surgery to be dependent on the magnitude of preoperative esotropia, whereas age, sex, AL, prior strabismus surgery and even additional MRR were not associated. Patients with larger esotropia underwent additional MRR more frequently, but we found no effect of MRR on the surgical outcomes.

First results on the procedure were published by the group of Yokoyama with results of 14 patients (23 eyes) (Yamaguchi et al. 2010) after their initial presentation of the surgical principle in 2000 (Yokoyama et al. 2000). Further studies comprising 7 to 25 patients were published (Akar et al. 2014; Fresina et al. 2014; Atili et al. 2016; Zou et al. 2017), as well as a few case reports and small case series (Wong et al. 2005; Rowe & Noonan 2006; Basmak et al. 2008; Durnian et al. 2010; Shih et al. 2012; Akbari et al. 2013; Su et al. 2016). Another Chinese study presented 16 patients, but details except the abstract could not be evaluated as the study was published in Chinese (Yang & Liu 2017). Hence, adding up patients with Yokoyama procedure from all publications so far, we found 108. Data of these studies are presented in Table 3.

Comparing our data with the literature (see Table 3), we confirm a good effect of the Yokoyama procedure procedure in a large group of patients with esohypotropia due to high myopia. Our patients had smaller mean preoperative esotropia than the initial study of Yamaguchi et al. (2010). This is partly due to the fact that there were six patients in our cohort with very small preoperative esotropia (four with typical ocular motility restriction and two with vertical angles of > 15°), but the potential effect of surgery on esotropia therefore was low in these patients in the first place.

On the other hand, we had fewer bilateral surgeries compared to the other studies with the Yokoyama technique and bilateral surgery tended to have a higher effect. Our data indicate that a large proportion of our patients had in fact bilateral high myopia, but had surgery only in one eye. We do not know the reasons for this in our data. For example, patients may not have had typical muscle and motility features of high myopes in their fellow eye or surgeons may have decided to operate one eye at a time with this rather new surgical technique. Nevertheless, 26 patients had further strabismus surgeries, two of them had Yokoyama surgery on the fellow eye. Our data seem to indicate that in bilateral high myopia, bilateral Yokoyama procedure has a larger effect than unilateral surgery, especially in patients with large preoperative angles, as overcorrection was generally rare and occurred in patients with smaller preoperative angles. In contrast, at least 35% of our patients with unilateral Yokoyama procedure had unilateral high myopia with an AL of less than 28 mm in the fellow eye. In the general population, unilateral high myopia is less frequent than bilateral disease (Weiss 2003). Data concerning prevalence in different populations are lacking, so we cannot rule out different prevalences concerning the East-Asian and European population.

Most studies agree about manifestation of this form of strabismus typically in a higher age group (see Table 3), although the results of Yokoyama procedure in three children have been published (Acar & Altintas 2015; Shenoy et al. 2015).

None of the other studies evaluated the effect of an additional MRR compared with pure Yokoyama procedure, probably due to the small number of individuals in each group. However, some studies indicate that MRR was performed when the forced duction test was suggestive of strong contracture of the MR or when it was technically difficult to perform muscle union of the superior rectus and LR muscles due to this restriction, as some surgeons in this study indicated as well (Yamaguchi et al. 2010; Akar et al. 2014).

Patients with additional MRR showed larger preoperative angles. This, however, was based on the surgeon's choice, who seem to have chosen MRR in case of large preoperative angles. Our data do not support an additional effect of MMR on our postoperative outcome measures.

We cannot conclude from our data whether MRR may have an additional effect when performed in a second surgery in case of insufficient effect of the first surgery.

Shenoy et al. (2015) published 15 patients (26 eyes), who received a modification of the original Yokoyama procedure: they used a silicone band

Table 3. Data of studies with more than ten patients with Yokoyama procedure

	n	Age [years]	Prior surgery	Uni/bilateral	MRR (eyes/patients) [mm]	Pre-op horizontal deviation	Post-op horizontal deviation
Yamaguchi 2010	14	63.8 ± 8.3	0	5/9	19/10 (5–8 mm, in 3 cases in a second surgery)	58.8° ± 36.0°	0.7° ± 9.0°
Akar 2014	20	34.8 ± 3.1	0	5/15		58.6**PD** ± 2.5**PD***	6.8**PD** ± 1.4**PD***
Fresina 2014	26	48.3 ± 15.8	0	19/7	33/26, 5–12 mm	46.2**PD** ± 15.5**PD***	7.36**PD** ± 9.09**PD***
Zou 2017	25	Median 46 (35–64)	0	17 (4 with Rec/res contralat)/8	29 / 21, 5–8 mm	42.6° ± 2.3° $^{+}$	6.3° ± 4.9° $^{+}$
Present study	133	59.7 ± 13.4	37/133	124/9	41/38 (2.5 to 12 mm)	23.8° ± 14.6°	8.7° ± 9.9°

In this study, we analysed all angles of strabismus and thus the effects of surgery in degree (°) and not in cm/m, as the unit degree represents the true eye position or change in position, respectively, and not its tangential projection (Basiakos et al. 2019)
* Recalculation of the data from cm/m in degree not possible, as individual pre- and postoperative angles not given in the paper,
$^{+}$ recalculated from the individual data in cm/m in the paper.

loop, which was sutured to the sclera. In two patients, the silicone band had to be removed due to foreign body sensation. However, results are not directly comparable, as one of the main advantages of the Yokoyama procedure is that there is no need of a scleral suture. Moreover, the mean age of patients was 27.9 years (±16 years); therefore, patients were younger than in most other publications. For comparison, mean preoperative esotropia was 36.8°±11.7° (range: 16–50°), which improved to 9.3°±9.3° (range: 0–27°) (recalculated from the original data in cm/m).

The need for a scleral suture in high myopic eyes is also the reason why the classical equatorial myopexy of the LR lost popularity in recent years, although the results of this surgery performed by experienced surgeons were satisfactory: for comparison, esotropia was reduced from 21.0°±15.0° to 3.2°±11.1° in 35 patients with a mean age of 60.3 ± 9.9 years by LR myopexy (superior border of LR only) combined with MRR (Gräf & Lorenz 2015).

The strength of our study is the large sample size with real-world clinical data on the Yokoyama procedure with and without additional MRR in a European population. We included 133 patients, which is much larger than all patients from the above-mentioned studies together. To our knowledge, this is the only study comparing these procedures on such a large-scale level. Due to different indications according to different centres, comparisons concerning additional procedures (especially MRR) or bilateral surgery were possible.

However, we need to acknowledge several limitations: as data were collected in a clinical setting, not all data sets were complete (especially AL, motility and MRI). Moreover, different sites may have different in-house standards considering the measurement of angles and indication or performance of surgery, although we could not find a relevant effect in our data.

In conclusion, to our knowledge this study provides data from the largest sample of patients with Yokoyama procedure and potential additional MRR. Patients with smaller preoperative esotropia had a higher probability of postoperative horizontal angles of ≤ 5 degrees and bilateral Yokoyama procedure appeared to have a higher effect in patients with bilateral myopic esohypotropia. An additional MRR may be helpful when MR restriction hampers adequate union of the superior rectus and LR, although MRR had no additional effect on our postoperative outcomes compared with the pure Yokoyama procedure and may lead to overcorrections. The Yokoyama procedure showed a higher effect (but also more residual esotropia) in patients with higher preoperative esotropia, indicating that the effect of this procedure mainly depends on the preoperative angle.

References

Acar Z & Altintas O (2015): Pediatric experience in surgical treatment of acquired esotropia associated with high myopia. J Pediatr Ophthalmol Strabismus **52**: article 191.

Akar S, Gokyigit B, Aribal E, Demir A, Goker YS & Demirok A (2014): Surgical procedure joining the lateral rectus and superior rectus muscles with or without medial rectus recession for the treatment of strabismus associated with high myopia. J Pediatr Ophthalmol Strabismus **51**: 53–58.

Akbari MR, Alhashemi LH, Jafari AK, Eshraghi B & Fakhraie G (2013): Large angle esotropia with high myopia and a lost medial rectus muscle: a case report. Binocul Vis Strabolog Q Simms Romano **28**: 110–114.

Aoki Y, Nishida Y, Hayashi O, Nakamura J, Oda S, Yamade S & Kani K (2003): Magnetic resonance imaging measurements of extraocular muscle path shift and posterior eyeball prolapse from the muscle cone in acquired esotropia with high myopia. Am J Ophthalmol **136**: 482–489.

Atili A, Singer E, Worz L & Olschewski N (2016): Small suture, large effect – THERAPY of esohypotropia associated with severe myopia. Klin Monbl Augenheilkd **233**: 1120–1123.

Basiakos S, Gräf M, Preising MN & Lorenz B. (2019): Splitting of the lateral rectus muscle with medial transposition to treat oculomotor palsy: a retrospective analysis of 29 consecutive cases. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie **257**: 2005–2014.

Basmak H, Sahin A & Yildirim N (2008): Surgical treatment of strabismus fixus associated with high myopia. Ophthalmic Surg Lasers Imaging **39**: 397–398.

Durnian JM, Maddula S & Marsh IB (2010): Treatment of "heavy eye syndrome" using simple loop myopexy. J AAPOS **14**: 39–41.

Fresina M, Finzi A, Versura P & Campos EC (2014): Muscle belly union associated with simultaneous medial rectus recession for treatment of myopic myopathy: results in 33 eyes. Eye (Lond) **28**: 557–561.

Godeiro KD, Kirsch D, Tabuse MK & Cronemberger M (2009): Yamada's surgery for treatment of myopic strabismus fixus. Int Ophthalmol **29**: 305–308.

Gräf M & Lorenz B (2015): Recess-resect surgery with myopexy of the lateral rectus muscle to correct esotropia with high myopia. Br J Ophthalmol **99**: 1702–1705.

Hayashi T, Iwashige H & Maruo T (1999): Clinical features and surgery for acquired progressive esotropia associated with severe myopia. Acta Ophthalmol Scand **77**: 66–71.

Herzau V & Ioannakis K (1996): Pathogenesis of eso- and hypotropia in high myopia. Klin Monbl Augenheilkd **208**: 33–36.

Kaynak S, Durak I, Ozaksoy D & Canda T (1994): Restrictive myopic myopathy: computed tomography, magnetic resonance imaging, echography, and histological findings. Br J Ophthalmol **78**: 414–415.

Kolling G (1993): Zur Genese der Schielabweichung bei hoher Myopie. Klin Mbl Augenheilk **151**.

Krzizok TH, Kaufmann H & Traupe H (1997): New approach in strabismus surgery in high myopia. Br J Ophthalmol **81**: 625–630.

Ranka MP & Steele MA (2015): Esotropia associated with high myopia. Curr Opin Ophthalmol **26**: 362–365.

Rowe FJ & Noonan CP (2006): Surgical treatment for progressive esotropia in the setting of high-axial myopia. J AAPOS **10**: 596–597.

Shenoy BH, Sachdeva V & Kekunnaya R (2015): Silicone band loop myopexy in the treatment of myopic strabismus fixus: surgical outcome of a novel modification. Br J Ophthalmol **99**: 36–40.

Shih MH, Li ML & Huang FC (2012): A preequatorial Gore-Tex sling to restore rectus muscle pathways in myopic strabismus fixus. J AAPOS **16**: 80–82.

Sturm V, Menke MN, Chaloupka K & Landau K (2008): Surgical treatment of myopic strabismus fixus: a graded approach. Graefes Arch Clin Exp Ophthalmol **246**: 1323–1329.

Su Y, Shen Q & Fan X (2016): Loop myopexy surgery for strabismus associated with high myopia. J Ophthalmol **2016**: 8657036.

Weiss AH (2003): Unilateral high myopia: optical components, associated factors, and visual outcomes. The British journal of ophthalmology **87**: 1025–1031.

Wong I, Leo SW & Khoo BK (2005): Loop myopexy for treatment of myopic strabismus fixus. J AAPOS **9**: 589–591.

Yamada M, Taniguchi S, Muroi T, Satofuka S & Nishina S (2002): Rectus eye muscle paths after surgical correction of convergent strabismus fixus. Am J Ophthalmol **134**: 630–632.

Yamaguchi M, Yokoyama T & Shiraki K (2010): Surgical procedure for correcting globe dislocation in highly myopic strabismus. Am J Ophthalmol **149**: 341–346.e2.

Yang GY & Liu LQ (2017): Efficacy of superior rectus and lateral rectus muscle belly union surgery for myopic Strabismus Fixus. Sichuan Da Xue Xue Bao Yi Xue Ban **48**: 779–782.

Yokoyama T, Tabuchi H, Ataka S, Shiraki K, Miki T & Mochizuki K (2000): The mechanism of development in progressive esotropia with high myopia. In: de Faber JT (ed.). Transactions of the 26th meeting of the European Strabismological Association. Lisse. Sweets & Zeitlinger: 218–221.

Zou L, Liu S, Liu R, Yao J, Liu Y, Lin J & Liu H (2017): Modified loop myopexy technique for severe high myopic strabismus fixus. Clin Exp Ophthalmol **45**: 790–796.

Received on July 3rd, 2020.
Accepted on February 2nd, 2021.

Correspondence:
Bettina WABBELS, MD
Department of Ophthalmology
University of Bonn
Ernst-Abbe-Str. 2
D-53127 Bonn, Germany
Tel: -49/ 228/ 287-15612
fax: -49/ 228/ 287-14692
Email: bettina.wabbels@ukbonn.de

The authors would like to thank H. Kerber (Frankfurt/M) and S. Knappe (Rostock) for providing additional patient data and Dr. T. Yokoyama (Osaka, Japan) for helpful discussions.

Mauschitz MM, Lohner V, Koch A, Stöcker T, Reuter M, Holz FG, Finger RP, Breteler MMB. **Retinal layer assessments as potential biomarkers for brain atrophy in the Rhineland Study**. Sci Rep. 2022 Feb 17;12(1):2757. DOI: 10.1038/s41598-022-06821-4

(*licensed under the Creative Commons Attribution 4.0 International License*)

Retinal assessments have been discussed as biomarkers for several neurodegenerative diseases as well as brain atrophy. However, available studies did not investigate all retinal layers due to older imaging technology, reported inconsistent results, or were based on small sample sizes. In this study, we included 2872 eligible participants of the Rhineland Study with data on SD-OCT and brain MRI. We used multiple linear regression to examine relationships between retinal measurements and volumetric brain measures as well as fractional anisotropy (FA) as measure of microstructural integrity of white matter (WM) for different brain regions.

In these 2872 participants, mean (SD) age was 53.8 ± 13.2 years (range 30-94) and 57% were women. Volumes of the inner retina were associated with total brain and grey matter (GM) volume, and even stronger with WM volume and FA. In contrast, the outer retina was mainly associated with GM volume, while both, inner and outer retina, were associated with hippocampus volume.

While we extend previously reported associations between the inner retina and brain measures, we found additional associations of the outer retina with parts of the brain. This indicates that easily accessible retinal SD-OCT assessments may serve as biomarkers for clinical monitoring of neurodegenerative diseases and merit further and longitudinal research.

www.nature.com/scientificreports

scientific reports

Check for updates

OPEN

Retinal layer assessments as potential biomarkers for brain atrophy in the Rhineland Study

Matthias M. Mauschitz[1,2], Valerie Lohner[1], Alexandra Koch[1], Tony Stöcker[3,4], Martin Reuter[5], Frank G. Holz[2], Robert P. Finger[2,7] & Monique M. B. Breteler[1,6,7]✉

Retinal assessments have been discussed as biomarkers for brain atrophy. However, available studies did not investigate all retinal layers due to older technology, reported inconsistent results, or were based on small sample sizes. We included 2872 eligible participants of the Rhineland Study with data on spectral domain–optical coherence tomography (SD–OCT) and brain magnetic resonance imaging (MRI). We used multiple linear regression to examine relationships between retinal measurements and volumetric brain measures as well as fractional anisotropy (FA) as measure of microstructural integrity of white matter (WM) for different brain regions. Mean (SD) age was 53.8 ± 13.2 years (range 30–94) and 57% were women. Volumes of the inner retina were associated with total brain and grey matter (GM) volume, and even stronger with WM volume and FA. In contrast, the outer retina was mainly associated with GM volume, while both, inner and outer retina, were associated with hippocampus volume. While we extend previously reported associations between the inner retina and brain measures, we found additional associations of the outer retina with parts of the brain. This indicates that easily accessible retinal SD-OCT assessments may serve as biomarkers for clinical monitoring of neurodegenerative diseases and merit further research.

The neurosensory retina and the brain derive from the same neural tissue, share morphologic and physiologic similarities and maintain direct synaptic connections over the whole life span[1]. To date, retinal layer thickness measurements with spectral domain–optical coherence tomography (SD–OCT) have become routine clinical biomarkers for ophthalmic diseases such as glaucoma[2,3]. Moreover, SD-OCT assessments are emerging as potential biomarkers for a variety of neurological and neurodegenerative diseases such as multiple sclerosis (MS) and dementia[4–8]. Previous studies reported associations between SD–OCT assessed retinal structures and magnetic resonance imaging (MRI) assessed brain parameters in small samples of mostly cognitively impaired participants[9,10]. Retinal imaging is non-invasive, easily assessable and less costly than MRI imaging, and therefore potentially suitable for mass screening. This, however, requires further elucidation of the relation of different retinal layers with brain features in the general population. To date, only one study evaluated the relation between retina layer parameters and the brain on a large-scale population level. This study used 1.5-Tesla (T) MRI which has since been superseded by the more advanced 3-T MRI. Furthermore, the authors concentrated on the inner retina and did not consider the outer retina due to technical limitations of retinal imaging at the time[11,12].

Nowadays, more advanced segmentation algorithms and higher resolution imaging enable the automated and precise identification of additional retinal layers including the outer retina as well as novel and more precise peripapillary retinal nerve fiber layer (pRNFL) parameters such as Bruch's membrane opening–minimum rim width (BMO–MRW) around the optic disk[13]. In addition, fractional anisotropy (FA) as assessed using diffusion tensor imaging (DTI), which is an indicator of white matter (WM) integrity, has recently been reported to correlate with disease severity in dementia and suggested as potential biomarker for neurodegeneration[14,15]. Thus, FA measures should be included in any future studies assessing the relationship between retinal and cerebral parameters.

[1]Population Health Sciences, German Center for Neurodegenerative Diseases (DZNE), Venusberg-Campus 1/99, 53127 Bonn, Germany. [2]Department of Ophthalmology, University Hospital Bonn, Bonn, Germany. [3]MR Physics, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany. [4]Department of Physics and Astronomy, University of Bonn, Bonn, Germany. [5]Image Analysis, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany. [6]Institute for Medical Biometry, Informatics and Epidemiology, Faculty of Medicine, University of Bonn, Bonn, Germany. [7]These authors contributed equally: Robert P. Finger and Monique M. B. Breteler. ✉email: Monique.Breteler@dzne.de

Against this background we investigated the association of all retinal layers as well as novel peripapillary RNFL parameters with cerebral structural measures, including DTI derived FA, in a general, mostly Caucasian, population.

Methods

Study population. This study is based on the Rhineland Study, a community based prospective cohort study to which all inhabitants of two geographically defined areas in the city of Bonn, Germany, who are 30 years of age or older, are being invited. Persons living in those areas are predominantly German with Caucasian ethnicity. Participation in the study is possible by invitation only. The only exclusion criterion is insufficient German language skills to give informed consent. The study adheres to the tenets of the Declaration of Helsinki and has approval of the ethical committee of the Medical Faculty of the University of Bonn. All participants gave written informed consent. Our analyses are based on individuals who completed MRI and SD–OCT data and have complete data on covariables. Furthermore, as these diseases may have an impact on retinal SD-OCT assessments or cause non-degenerative brain changes, we excluded participants with a self-reported history of stroke, multiple sclerosis (MS), glaucoma, and macular degeneration or missing data on this (n = 50, n = 19, n = 62, and n = 75, respectively).

Ophthalmic assessments and covariates. We assessed retinal layers of the right eye with our previously reported protocol using the Spectralis SD–OCT (Heidelberg Engineering, Heidelberg, Germany)[13]. In short, the in-built segmentation algorithms of the Heidelberg Eye Explorer (HEYEX) enables the automatic delineation of all macular layers including the outer retina: the inner retinal layers comprise the retinal nerve fiber layer (mRNFL), ganglion cell layer (mGCL), inner plexiform layer (mIPL), and inner nuclear layer (mINL). The outer retinal layers include the outer plexiform layer (mOPL), outer nuclear layer (mONL), and retinal pigment epithelium (mRPE). Around the optic disc, the algorithm delineates pRNFL and BMO–MRW which has shown good agreement with manual segmentation[16]. As initial quality assurance process, we filtered out large outliers and manually checked them. We excluded cases of pathology (e.g. epiretinal membrane) that deteriorate the reliability of the assessments. Refraction and best-corrected visual acuity (BCVA) were measured with an automated refractometer (Ark-1s, NIDEK CO., Tokyo, Japan). IOP was measured using non-contact tonometry (TX-20, Canon, Tokyo, Japan). Spherical equivalent (SE) was calculated as the spherical value and half of the cylindrical value. In absence of contraindications, participants were dilated for imaging using standard mydriatic agents (tropicamide and phenylephrine)[13]. Hypertension was defined as measured systolic blood pressure (SBP) > 139 mmHg and/or diastolic blood pressure (DBP) > 89 mmHg and/or use of antihypertensive drugs; diabetes was defined as measured fasting glycated hemoglobin (HbA1c) > 6.5% and/or the use of antidiabetic drugs. Body-mass-index (BMI) was defined as measured body weight (in kilogram) divided by square body height (in meters).

Structural brain MRI. We performed MRI using a 3-T Siemens MAGNETOM Prisma MRI scanner (Siemens Healthcare, Erlangen, Germany) in absence of contraindications. Whole brain T1-weighted multi-echo magnetisation prepared rapid gradient-echo (MEMPRAGE, 0.8 mm isotropic resolution)[17,18] images were acquired on two 3-T Siemens MAGNETOM Prisma MRI scanners (Siemens Healthcare, Erlangen, Germany) in absence of contraindications. Total brain volume (TBV), total hippocampal volume (THV) as well as total and occipital grey (GM) and white matter (WM) volumes, based on the Desikan-Killiany atlas, were automatically determined using FreeSurfer version 6.0, which has been shown to be extremely reliable with excellent test–retest intraclass correlation coefficients across different MRI scanners and sequences[19,20].

Diffusion MRI. Simultaneous-multi-slice diffusion weighted MRI (dMRI) was performed with a spin-echo echoplanar imaging (SE-EPI) sequence applying threefold slice-acceleration[21–23]. A compressed sensing[24] diffusion spectrum imaging[25] (CS-DSI) protocol[26] was used to collect dMRI scans at 1.5 mm isotropic spatial resolution. After correction of susceptibility-induced[27] and eddy-current-induced geometric distortions and subject motion[26,28] using FSL version 6.0 (www.fmrib.ox.ac.uk/fsl) and after CS reconstruction[26,29], fractional anisotropy (FA) was obtained from the diffusion tensor model[30] using the MDT framework[31]. The Freesurfer processed T1-weighted MR image was used to generate a whole brain WM mask, which was further corrected for WM hyperintensities obtained from a T2- weighted FLAIR image, thresholded at an FA value of 0.3, constrained to avoid partial voluming with CSF[32] and refined through FA skeletonization. Applying this mask, global FA values were computed as the average across voxels within normal appearing WM. Additionally, a WM tract-specific mean FA measure was derived for the optic radiation provided by the Jülich histological atlas[33].

Data analyses. Of the first 5000 participants, 3505 underwent MRI. Of these, 3395 participants had complete data on SD–OCT, and 3113 on all (co-)variables. The most frequent reason for missing SD–OCT data was technical issues, followed by low compliance during imaging resulting in low image quality. SD-OCT scans of 35 participants did not meet our predefined minimum quality standard of ≥ 20 dB signal strength (out of possible 40 dB) and hence were excluded from the analyses, leaving us with 2872 participants for final analyses. FA data for global WM and for the optic radiation were available in 2797 participants.

We used multivariable regression analyses to quantify the relations between SD-OCT measurements of specific retinal layers and MRI derived brain assessments. For ease of comparison, we standardized the different brain parameters. Hence, the regression models indicate percentage of difference in volume for each cerebral parameter. Moreover, we calculated beta-coefficients for each retinal layer per unit (mm^3 and µm, respectively) as well as per standard deviation (SD). We adjusted for several previously reported confounders and determinants of retinal

	Mean ± SD or n(%)
Age (years)	53.8 ± 13.2
Women	1649 (57.4%)
Spherical equivalent (dpt)	− 0.65 ± 2.5
Body-Mass-Index (kg/m²)	25.6 ± 4.2
Smoking status	
Never	1390 (48.4%)
Former	1103 (38.4%)
Current	379 (13.2%)
Hypertension	980 (34%)
Diabetes mellitus	116 (4%)
Brain volumetric parameters (in ml)	
Total brain	1111.0 ± 116.1
Total grey matter	461.2 ± 47.5
Total white matter	458.2 ± 57.8
Occipital grey matter	48.3 ± 6.2
Occipital white matter	42.4 ± 6.2
Hippocampi	7.92 ± 0.9
Fractional anisotropy (FA) of total white matter[a]	0.629 ± 0.02
FA of WM of the optic radiation[a]	0.628 ± 0.02
Macular volumetric parameters (in mm³)	
Retinal nerve fiber layer (mRNFL)	0.95 ± 0.12
Ganglion cell layer (mGCL)	1.08 ± 0.10
Inner plexiform layer (mIPL)	0.89 ± 0.07
Inner nuclear layer (mINL)	0.95 ± 0.06
Outer plexiform layer (mOPL)	0.82 ± 0.07
Outer nuclear layer (mONL)	1.73 ± 0.19
Retinal pigment epithelium (mRPE)	0.39 ± 0.04
Total retina	8.66 ± 0.39
Optic disc thickness parameters (in microns)	
Peripapillary retinal nerve fiber layer (pRNFL)	100.0 ± 10.8
Bruch's membrane opening–minimum rim width (BMO–MRW)	341.3 ± 61.3

Table 1. Characteristics of participants included in the analyses (n = 2872). [a]n = 2797.

SD-OCT assessments[13,34]. Multivariable regression models included the brain assessments as outcome and the respective retinal layer as independent variable and were adjusted for age, sex, SE, estimated total intracranial volume (eTIV), BMI, hypertension, diabetes, and smoking. All analyses were performed with the statistical software RStudio (R version 4.0.3, RStudio, Inc, Boston, MA, https://www.rstudio.com/).

Results

Compared to participants who underwent MRI (n = 3505), those without MRI data (n = 1495) were slightly older (57.7 ± 14.6 vs. 54.8 ± 13.6 years), included less women (52.9% vs. 58.0%), and showed a more positive SE (− 0.55 ± 2.6 vs. − 0.67 ± 2.6 diopters). The 2872 participants that were included in our final analysis showed similar age (53.8 ± 13.2 years), sex distribution (57.4% women), and SE (− 0.65 ± 2.5 diopters; Table 1), as the total group of participants with MRI.

All inner and outer retinal layers except for mONL were positively associated with total brain volume (TBV). The associations were most outspoken for the inner retina, and stronger with WM than with GM volume (see beta-coefficients in Table 2). We saw a similar pattern of associations between retinal layers and occipital lobe volumes, with the estimates being even stronger than for total brain volumes (see beta-coefficients in Table 3). The inner retina around the optic nerve head (pRNFL and BMO–MRW) was similarly associated with brain volumetric measures as the macular inner retina. The mRPE, as part of the outer retina, was strongly associated with TBV and GM, but not with WM volume. The pattern of associations between retinal layer measures and the hippocampi, was similar to what we observed for total brain volumes, but relative effect sizes were much larger (Table 3). We found no association of mONL with any brain volume. Regarding the DTI analyses, mainly the inner retina showed positive associations with FA of normal appearing WM. This association was even stronger for FA of the optic radiation (see beta-coefficients in Table 4). As sensitivity analyses, we repeated all models stratified by age above and below 58 years (data not shown). We found similar, although smaller associations and some weaker associations vanished, particularly in the older group, in which we additionally found an association of ONL with total WM.

	Total brain volume			Total grey matter volume			Total white matter volume		
	Difference (%) per mm^3/µm [95% CI]	Difference (%) per SD [95% CI]	p	Difference (%) per mm^3/µm [95% CI]	Difference (%) per SD [95% CI]	p	Difference (%) per mm^3/µm [95% CI]	Difference (%) per SD [95% CI]	p
mRNFL	1.58 [0.43; 2.74]	0.19 [0.05; 0.33]	0.007	0.34 [-1.04; 1.72]	0.04 [-0.13; 0.21]	0.63	2.89 [1.01; 4.76]	0.35 [0.12; 0.58]	0.002
mGCL	7.08 [5.61; 8.55]	0.70 [0.56; 0.85]	< 0.001	5.45 [3.67; 7.22]	0.54 [0.37; 0.72]	< 0.001	8.58 [6.17; 10.99]	0.86 [0.62; 1.10]	< 0.001
mIPL	8.61 [6.68; 10.55]	0.64 [0.49; 0.78]	< 0.001	6.94 [4.60; 9.27]	0.51 [0.34; 0.69]	< 0.001	9.89 [6.72; 13.07]	0.73 [0.50; 0.97]	< 0.001
mINL	3.17 [0.96; 5.39]	0.21 [0.06; 0.35]	0.005	0.85 [-1.80; 3.50]	0.05 [-0.12; 0.23]	0.53	4.46 [0.86; 8.06]	0.29 [0.05; 0.52]	0.02
mOPL	2.76 [0.87; 4.66]	0.20 [0.06; 0.33]	0.004	2.11 [-0.15; 4.38]	0.15 [-0.01; 0.31]	0.07	3.37 [0.28; 6.45]	0.24 [0.02; 0.46]	0.03
mONL	0.41 [-0.33; 1.15]	0.07 [-0.06; 0.22]	0.28	0.73 [-0.16; 1.62]	0.14 [-0.03; 0.31]	0.10	-0.24 [-1.45; 0.96]	-0.04 [-0.27; 0.18]	0.69
mRPE	5.89 [2.01; 9.77]	0.21 [0.07; 0.34]	0.003	6.59 [1.95; 11.22]	0.23 [0.07; 0.40]	0.005	3.99 [-2.33; 10.31]	0.14 [-0.08; 0.36]	0.22
pRNFL	0.04 [0.03; 0.06]	0.49 [0.35; 0.64]	< 0.001	0.02 [0.01; 0.04]	0.25 [0.08; 0.42]	0.004	0.06 [0.04; 0.08]	0.61 [0.38; 0.84]	< 0.001
BMO–MRW	0.00 [0.00; 0.01]	0.25 [0.10; 0.39]	< 0.001	0.00 [0.00; 0.00]	0.00 [-0.18; 0.16]	0.92	0.01 [0.00; 0.01]	0.42 [0.19; 0.65]	< 0.001

Table 2. Associations of retinal layers with brain volumetric parameters (n = 2872). *mRNFL* macular retinal nerve fiber layer, *mGCL* macular ganglion cell layer, *mIPL* macular inner plexiform layer, *mINL* macular inner nuclear layer, *mOPL* macular outer plexiform layer, *mONL* macular outer nuclear layer, *mRPE* macular retinal pigment epithelium, *pRNFL* peripapillary RNFL, *BMO–MRW* Bruch's membrane opening–minimum rim width. Macular layer volumes per mm^3; pRNFL and BMO–MRW per µm.

	Occipital grey matter volume			Occipital white matter volume			Total hippocampal volume		
	Difference (%) [95% CI] per mm^3/µm	Difference (%) per SD [95% CI]	p	Difference (%) [95% CI] per mm^3/µm	Difference (%) per SD [95% CI]	p	Difference (%) per mm^3/µm [95% CI]	Difference (%) per SD [95% CI]	p
mRNFL	2.41 [-0.50; 5.31]	0.29 [-0.06; 0.64]	0.10	5.93 [2.53; 9.35]	0.72 [0.31; 1.14]	< 0.001	2.64 [0.14; 5.13]	0.32 [0.02; 0.62]	0.04
mGCL	12.47 [8.74; 16.20]	1.24 [0.87; 1.62]	< 0.001	15.00 [10.61; 19.39]	1.50 [1.06; 1.93]	< 0.001	13.27 [10.08; 16.47]	1.32 [1.01; 1.64]	< 0.001
mIPL	13.77 [8.86; 18.68]	1.02 [0.66; 1.38]	< 0.001	15.18 [9.40; 20.97]	1.13 [0.70; 1.55]	< 0.001	17.46 [13.26; 21.65]	1.29 [0.98; 1.60]	< 0.001
mINL	-1.95 [-7.53; 3.63]	-0.13 [-0.49; 0.24]	0.49	2.35 [-5.50; 8.91]	0.15 [-0.27; 0.58]	0.43	6.94 [2.16; 11.73]	0.45 [0.14; 0.76]	0.004
mOPL	-0.32 [-5.10; 4.45]	-0.02 [-0.37; 0.32]	0.89	0.11 [-7.34; 5.73]	0.00 [-0.01; 0.01]	0.97	5.78 [1.68; 9.88]	0.42 [0.12; 0.71]	0.005
mONL	1.74 [-0.12; 3.61]	0.33 [-0.02; 0.69]	0.07	-0.10 [-2.30; 2.09]	-0.02 [-0.04; 0.04]	0.93	-0.25 [-1.86; 1.35]	-0.05 [-0.35; 0.26]	0.76
mRPE	4.51 [-5.29; 14.29]	0.16 [-0.19; 0.50]	0.37	3.68 [-7.83; 15.18]	0.13 [-0.28; 0.54]	0.53	11.14 [2.75; 19.54]	0.39 [0.10; 0.69]	0.009
pRNFL	0.14 [0.11; 0.17]	1.49 [1.13; 1.84]	< 0.001	0.19 [0.15; 0.22]	2.00 [1.59; 2.41]	< 0.001	0.10 [0.07; 0.13]	1.06 [0.76; 1.39]	< 0.001
BMO–MRW	0.01 [0.00; 0.01]	0.56 [0.21; 0.92]	0.02	0.02 [0.01; 0.02]	0.96 [0.54; 1.38]	< 0.001	0.01 [0.00; 0.01]	0.48 [0.17; 0.78]	0.002

Table 3. Associations of retinal layers with occipital and hippocampal volumetric parameters (n = 2872). *mRNFL* macular retinal nerve fiber layer, *mGCL* macular ganglion cell layer, *mIPL* macular inner plexiform layer, *mINL* macular inner nuclear layer, *mOPL* macular outer plexiform layer, *mONL* macular outer nuclear layer, *mRPE* macular retinal pigment epithelium, *pRNFL* peripapillary RNFL, *BMO–MRW* Bruch's membrane opening–minimum rim width. Macular layer volumes per mm^3; pRNFL and BMO–MRW per µm.

	FA total white matter			FA optic radiation		
	Difference (%) per mm^3/µm [95% CI]	Difference (%) per SD [95% CI]	p	Difference (%) per mm^3/µm [95% CI]	Difference (%) per SD [95% CI]	p
mRNFL	0.25 [-0.11; 1.40]	0.08 [-0.01; 0.17]	0.09	2.72 [1.62; 3.82]	0.33 [0.20; 0.46]	< 0.001
mGCL	2.31 [1.34; 3.28]	0.23 [0.13; 0.27]	< 0.001	6.38 [4.98; 7.78]	0.64 [0.50; 0.78]	< 0.001
mIPL	2.92 [1.64; 4.19]	0.22 [0.12; 0.31]	< 0.001	7.22 [5.37; 9.07]	0.53 [0.40; 0.67]	< 0.001
mINL	1.88 [0.43; 3.32]	0.12 [0.03; 0.22]	0.01	3.01 [0.90; 5.13]	0.20 [0.06; 0.33]	0.005
mOPL	1.29 [0.05; 2.52]	0.09 [0.01; 0.18]	0.04	1.85 [0.04; 3.66]	0.13 [0.00; 0.26]	0.05
mONL	0.34 [-0.15; 0.82]	0.06 [-0.03; 0.16]	0.17	0.85 [0.14; 1.56]	0.16 [0.03; 0.30]	0.02
mRPE	-0.30 [-2.84; 2.24]	-0.01 [-0.10; 0.08]	0.82	1.01 [-2.71; 4.72]	0.04 [-0.10; 0.17]	0.60
pRNFL	0.01 [0.00; 0.02]	0.14 [0.04; 0.23]	0.004	0.06 [0.04; 0.07]	0.59 [0.46; 0.73]	< 0.001
BMO–MRW	0.00 [-0.01; 0.01]	-0.08 [-0.17; 0.01]	0.10	0.00 [0.00; 0.00]	0.06 [-0.07; 0.20]	0.36

Table 4. Associations of retinal layers with white matter fractional anisotropy (n = 2797). *FA* fractional anisotropy, *mRNFL* macular retinal nerve fiber layer, *mGCL* macular ganglion cell layer, *mIPL* macular inner plexiform layer, *mINL* macular inner nuclear layer, *mOPL* macular outer plexiform layer, *mONL* macular outer nuclear layer, *mRPE* macular retinal pigment epithelium, *pRNFL* peripapillary RNFL, *BMO–MRW* Bruch's membrane opening-minimum rim width. Macular layer volumes per mm^3; pRNFL and BMO–MRW per µm.

Discussion

We found associations of volume/thickness of inner retinal layers with TBV, which seemed to be primarily driven by a relationship with WM. These associations were even stronger within the occipital lobe and with the hippocampus, and were also found in the inner retina around the optic disc (pRNFL and BMO–MRW). That the relation was primarily with WM was supported by our finding of significant relationships between those layers with DTI parameters of WM integrity. In contrast, we observed a relation of parts of the outer retina with TBV, which seemed to be due to an association with GM. Our data suggest SD-OCT-derived retinal assessments can potentially serve as biomarkers of cerebral atrophy.

Most of the few published studies on the relation of MRI brain assessments and OCT-derived retinal layer measurements were based on small cohorts of selected participants and included both, neurologically healthy and diseased individuals. These studies reported diverse and partially conflicting results on the relation of the inner retina, mostly pRNFL and mGCL, and different cerebral areas[9,10,35,36]. The limited power in, and the huge methodological differences between, most of these studies, however, hinders drawing strong conclusions on the basis of their results.

The only population-based study that we are aware of that reported on the relation between retinal measures and brain features, is the Rotterdam Study[11,12]. This study found strong associations of the innermost retinal layers (mainly pRNFL and mGCL and to some extent mIPL) with both, GM and WM volumes and partly with FA as assessed using DTI[11,12]. However, in the Rotterdam Study, segmentation algorithms were only able to distinguish the inner retina. In their analysis, the mIPL was the most outer, and thus potentially least precisely, segmented layer. Our data corroborate their findings, and extend those in that we found strong associations of mIPL with all cerebral assessments and additionally of mINL as further inner layer with TBV. Hence, we found that various layers of the inner retina both at the macula and the optic disc were associated with brain volumes, especially with WM volume.

We were able to also segment the outer retina, and found that the mRPE was associated with TBV, which seemed specifically driven by GM. We are only aware of two small studies that investigated the relation of the outer retina with MRI brain parameters. One study found no relation in 52 participants[37], whereas the other study found that the outer retina was associated with TBV in 64 participants[38]. However, besides the small sample sizes, these studies did not delineate all retinal layers and only adjusted for age and sex as potential confounders within their analyses. Our findings therefore need confirmation from larger, methodologically robust studies.

A question is what underlies our findings. That we found the strongest associations for the inner retina may indicate that ganglion cells and their inter-connections (both, distal axons and proximal dendrites) decline in case of cerebral deterioration/changes. Previous studies hypothesized retrograde degeneration as a potential pathomechanism, leading from cortical atrophy via reduced neuronal inter-connections to decline of retinal axons[4,12,34]. However, this pathomechanism appears less likely for the outer retina. Here, systemic changes e.g. associated with impaired perfusion or vasculopathy may play a role. The mRPE is a thin layer of highly metabolically active cells supporting photoreceptors in the maintenance of the visual cycle, contributes to the blood-retina barrier[39] and is not part of the neuro-sensory retina with direct connection to cerebral neurons. This may explain why we found no association of mRPE with WM volumes as we did for the inner retina. While associations of the neuro-sensory (inner) retina with the brain can be explained by the close anatomical connection, we speculate that the observed associations of mRPE are less direct and represent a more general metabolic dysregulation. Interestingly, we found no relation of the mONL with any cerebral assessment. The mONL represents a large layer between the inner retina and the mRPE and consists of parts of the photoreceptors. The lack of any association therefore suggests that photoreceptors, as the first cells within the visual afferent pathway, are relatively unaffected by cerebral changes.

We found the strongest associations, both for inner and outer retinal layers, with volumes of the hippocampi. Only few, small studies reported correlations of retinal measurements with hippocampus volumes and suggested these to be potential biomarkers of neurodegeneration[40–42]. As hippocampus volumes decrease early in cognitive impairment[43], retinal assessments may be an easily accessible biomarker of hippocampus atrophy and cognitive decline[44]. Our data suggest that in clinical routine, SD-OCT assessments of retinal layers may be useful as additional examination in the longitudinal monitoring of neurological/neurodegenerative diseases, which e.g. has already been proposed for MS[45].

Apart from structural measurements, we found various layers of the inner retina to be associated with FA, a proxy measure for WM microstructural integrity. As expected, effects were larger in the optic radiation as compared to total WM. This adds to and extends the results of the Rotterdam Study, which reported only the innermost layers (pRNFL and mGCL) to be associated with FA[12].

To our knowledge, our study is the first to report on the relation of fully segmented retinal layers and various cerebral parameters from structural MRI and DTI in a large, general Caucasian population. The strengths of our study include the large community-based population with a wide age range from 30 to 94 years. The weaker associations in the sensitivity analysis are likely due to the reduced sample size and, in the older group, the general decrease in retinal layer thickness with age, which leads to smaller absolute differences and likely reduced accuracy in detecting changes. Moreover, we hypothesize the association of ONL with total WM to be spurious, as the ONL contains cell bodies, which are not likely directly connected to the axons of WM and we found no association of ONL with any MRI assessment in the total cohort. The study protocol comprised comprehensive and standardized ocular, MRI-based cerebral and systemic deep phenotyping. SD-OCT and MRI imaging were performed using a state-of-the-art device with high resolution scans and automated layer segmentation, including the deeper outer retinal layers[13]. For MRI image analysis we performed post-processing based on well-established atlases. Moreover, we adjusted our analyses for several ocular confounders, which has not been the case in many neurological studies on SD-OCT. Yet, several limitations must be considered. Even

though participation was possible by invitation only, a self-selection of younger and more healthy participants may have occurred. Hence, our study population is not strictly representative of the entire German population. To the extent that this may have introduced bias, we consider it most likely that it led to an underestimation of effects. Furthermore, information on some diseases was self-reported which may have been less reliable than medical diagnoses. We did not manually check the retinal layer segmentation of all scans, but we excluded scans below a strict quality threshold. It is therefore unlikely, also given the large sample size, that remaining segmentation artefacts have confounded our results to any relevant extent[13]. Lastly, we performed a number of statistical models, which may have increased alpha error accumulation. However, we consider beta-coefficients and respective confidence intervals much more important than p-values as a binary cut-off in this exploratory study. The widely used Bonferroni correction (in our study $0.05/72 \approx 0.00069$) has frequently been reported to be over-conservative causing too many false negatives[46]. Hence, we report beta-coefficients, confidence intervals, and p-values so that the reader is able to evaluate both statistical significance and clinical relevance. In conclusion, we found strong associations of the inner and outer retina with various cerebral structures. Our study implies that SD-OCT assessments of different retinal layers may serve as potential biomarkers for cerebral atrophy and may aid in neurodegenerative disease monitoring. Further research to evaluate the value of SD-OCT assessments of the retina in detecting or monitoring cerebral changes and neurodegenerative diseases is warranted.

Data availability

The datasets analyzed during the current study are not publicly available due to participant privacy, but may be available from the corresponding author on reasonable request.

Received: 31 August 2021; Accepted: 20 January 2022
Published online: 17 February 2022

References

1. Chang, L. Y. L. *et al.* Alzheimer's disease in the human eye. Clinical tests that identify ocular and visual information processing deficit as biomarkers. *Alzheimer's Dementia J. Alzheimer's Assoc.* **10**, 251–261 (2014).
2. Mwanza, J.-C., Oakley, J. D., Budenz, D. L. & Anderson, D. R. Ability of cirrus HD-OCT optic nerve head parameters to discriminate normal from glaucomatous eyes. *Ophthalmology* **118**, 241–8.e1 (2011).
3. Gardiner, S. K., Fortune, B. & Demirel, S. Localized changes in retinal nerve fiber layer thickness as a predictor of localized functional change in glaucoma. *Am. J. Ophthalmol.* **170**, 75–82 (2016).
4. Mutlu, U. *et al.* Association of retinal neurodegeneration on optical coherence tomography with dementia. A population-based study. *JAMA Neurol.* **75**, 1256–1263 (2018).
5. Jones-Odeh, E. & Hammond, C. J. How strong is the relationship between glaucoma, the retinal nerve fibre layer, and neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis?. *Eye (Lond.)* **29**, 1270–1284 (2015).
6. Britze, J. & Frederiksen, J. L. Optical coherence tomography in multiple sclerosis. *Eye (Lond.)* **32**, 884–888 (2018).
7. Balk, L. J. *et al.* Timing of retinal neuronal and axonal loss in MS. A longitudinal OCT study. *J. Neurol.* **263**, 1323–1331 (2016).
8. Chan, V. T. T. *et al.* Spectral-domain OCT measurements in Alzheimer's disease: A systematic review and meta-analysis. *Ophthalmology* **126**, 497–510 (2019).
9. Ong, Y.-T. *et al.* Retinal neurodegeneration on optical coherence tomography and cerebral atrophy. *Neurosci. Lett.* **584**, 12–16 (2015).
10. Casaletto, K. B. *et al.* Retinal thinning is uniquely associated with medial temporal lobe atrophy in neurologically normal older adults. *Neurobiol. Aging* **51**, 141–147 (2017).
11. Mutlu, U. *et al.* Retinal neurodegeneration and brain MRI markers: The Rotterdam Study. *Neurobiol. Aging* **60**, 183–191 (2017).
12. Mutlu, U. *et al.* Thinner retinal layers are associated with changes in the visual pathway. A population-based study. *Hum. Brain Map.* **39**, 4290–4301 (2018).
13. Mauschitz, M. M., Holz, F. G., Finger, R. P. & Breteler, M. M. B. Determinants of macular layers and optic disc characteristics on SD-OCT. The Rhineland study. *Transl. Vis. Sci. Technol.* **8**, 34 (2019).
14. Kantarci, K. *et al.* White-matter integrity on DTI and the pathologic staging of Alzheimer's disease. *Neurobiol. Aging* **56**, 172–179 (2017).
15. Fischer, F. U., Wolf, D., Scheurich, A. & Fellgiebel, A. Altered whole-brain white matter networks in preclinical Alzheimer's disease. *NeuroImage. Clin.* **8**, 660–666 (2015).
16. Wong, B. M. *et al.* Validation of optical coherence tomography retinal segmentation in neurodegenerative disease. *Transl. Vis. Sci. Technol.* **8**, 6 (2019).
17. Brenner, D., Stirnberg, R., Pracht, E. D. & Stöcker, T. Two-dimensional accelerated MP-RAGE imaging with flexible linear reordering. *Magma (New York, N.Y.)* **27**, 455–462 (2014).
18. van der Kouwe, A. J. W., Benner, T., Salat, D. H. & Fischl, B. Brain morphometry with multiecho MPRAGE. *Neuroimage* **40**, 559–569 (2008).
19. Desikan, R. S. *et al.* An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* **31**, 968–980 (2006).
20. Morey, R. A. *et al.* Scan–rescan reliability of subcortical brain volumes derived from automated segmentation. *Hum. Brain Mapp.* **31**, 1751–1762 (2010).
21. Setsompop, K. *et al.* Blipped-controlled aliasing in parallel imaging for simultaneous multislice echo planar imaging with reduced g-factor penalty. *Magn. Reson. Med.* **67**, 1210–1224 (2012).
22. Xu, J. *et al.* Evaluation of slice accelerations using multiband echo planar imaging at 3 T. *Neuroimage* **83**, 991–1001 (2013).
23. Cauley, S. F., Polimeni, J. R., Bhat, H., Wald, L. L. & Setsompop, K. Interslice leakage artifact reduction technique for simultaneous multislice acquisitions. *Magn. Reson. Med.* **72**, 93–102 (2014).
24. Menzel, M. I. *et al.* Accelerated diffusion spectrum imaging in the human brain using compressed sensing. *Magn. Reson. Med.* **66**, 1226–1233 (2011).
25. van Wedeen, J., Hagmann, P., Tseng, W.-Y.I., Reese, T. G. & Weisskoff, R. M. Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magn. Reson. Med.* **54**, 1377–1386 (2005).
26. Tobisch, A. *et al.* Compressed sensing diffusion spectrum imaging for accelerated diffusion microstructure MRI in long-term population imaging. *Front. Neurosci.* **12**, 650 (2018).
27. Andersson, J. L. R., Skare, S. & Ashburner, J. How to correct susceptibility distortions in spin-echo echo-planar images: Application to diffusion tensor imaging. *Neuroimage* **20**, 870–888 (2003).

28. Andersson, J. L. R. & Sotiropoulos, S. N. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *Neuroimage* **125**, 1063–1078 (2016).
29. Tobisch, A. *et al.* Comparison of basis functions and q-space sampling schemes for robust compressed sensing reconstruction accelerating diffusion spectrum imaging. *NMR Biomed.* **32**, e4055 (2019).
30. Basser, P. J., Mattiello, J. & LeBihan, D. MR diffusion tensor spectroscopy and imaging. *Biophys. J.* **66**, 259–267 (1994).
31. Harms, R. L., Fritz, F. J., Tobisch, A., Goebel, R. & Roebroeck, A. Robust and fast nonlinear optimization of diffusion MRI microstructure models. *Neuroimage* **155**, 82–96 (2017).
32. Jeurissen, B., Leemans, A., Tournier, J.-D., Jones, D. K. & Sijbers, J. Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Hum. Brain Mapp.* **34**, 2747–2766 (2013).
33. Bürgel, U. *et al.* White matter fiber tracts of the human brain: Three-dimensional mapping at microscopic resolution, topography and intersubject variability. *Neuroimage* **29**, 1092–1105 (2006).
34. Mauschitz, M. M. *et al.* Systemic and ocular determinants of peripapillary retinal nerve fiber layer thickness measurements in the European Eye Epidemiology (E3) population. *Ophthalmology* **125**, 1526–1536 (2018).
35. Shi, Z. *et al.* Retinal nerve fiber layer thinning is associated with brain atrophy: A longitudinal study in nondemented older adults. *Front. Aging Neurosci.* **11**, 69 (2019).
36. Sung, M. S. *et al.* Inner retinal thinning as a biomarker for cognitive impairment in de novo Parkinson's disease. *Sci. Rep.* **9**, 11832 (2019).
37. Jorge, L., Canário, N., Quental, H., Bernardes, R. & Castelo-Branco, M. Is the retina a mirror of the aging brain? Aging of neural retina layers and primary visual cortex across the lifespan. *Front. Aging Neurosci.* **11**, 360 (2019).
38. Uchida, A. *et al.* Correlation between brain volume and retinal photoreceptor outer segment volume in normal aging and neurodegenerative diseases. *PloS One* **15**, e0237078 (2020).
39. Vinores, S. A. Assessment of blood-retinal barrier integrity. *Histol. Histopathol.* **10**, 141–154 (1995).
40. Shi, Z. *et al.* Retinal nerve fiber layer thickness is associated with hippocampus and lingual gyrus volumes in nondemented older adults. *Prog. Neuro Psychopharm. Biol. Psychiatry* **99**, 109824 (2020).
41. Méndez-Gómez, J. L. *et al.* Association of retinal nerve fiber layer thickness with brain alterations in the visual and limbic networks in elderly adults without dementia. *JAMA Netw. Open* **1**, e184406 (2018).
42. Tao, R. *et al.* Perifovea retinal thickness as an ophthalmic biomarker for mild cognitive impairment and early Alzheimer's disease. *Alzheimer's Dementia (Amsterdam, Netherlands)* **11**, 405–414 (2019).
43. Tabatabaei-Jafari, H., Shaw, M. E. & Cherbuin, N. Cerebral atrophy in mild cognitive impairment: A systematic review with meta-analysis. *Alzheimer's Dementia (Amsterdam, Netherlands)* **1**, 487–504 (2015).
44. Ward, D. D. *et al.* Association of retinal layer measurements and adult cognitive function: A population-based study. *Neurology* **95**, e1144–e1152 (2020).
45. Petzold, A. *et al.* Retinal layer segmentation in multiple sclerosis: A systematic review and meta-analysis. *Lancet. Neurol.* **16**, 797–812 (2017).
46. Perneger, T. V. What's wrong with Bonferroni adjustments. *BMJ (Clin. Res. ed.)* **316**, 1236–1238 (1998).

Author contributions

Conceptualization: M.M.M., R.P.F., M.M.B.B.; methodology: M.M.M., R.P.F., M.M.B.B., V.L., A.K.; Statistical analysis: M.M.M., R.P.F., M.M.B.B.; writing—original draft preparation: M.M.M., R.P.F., M.M.B.B.; writing—review and editing: V.L., A.K., T.S., M.R., F.G.H.; all authors have read and agreed to the published version of the manuscript.

Funding

Open Access funding enabled and organized by Projekt DEAL.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to M.M.B.B.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022

Mauschitz MM, Schmitz MT, Verzijden T, Schmid M, Thee EF, Colijn JM, Delcourt C, Cougnard-Grégoire A, Merle BMJ, Korobelnik JF, Gopinath B, Mitchell P, Elbaz H, Schuster AK, Wild PS, Brandl C, Stark KJ, Heid IM, Günther F, Peters A, Klaver CCW, Finger RP; European Eye Epidemiology (E3) Consortium. **Physical Activity, Incidence, and Progression of Age-Related Macular Degeneration: A Multicohort Study.** Am J Ophthalmol. 2022 Apr;236:99-106. DOI: 10.1016/j.ajo.2021.10.008

In this study, we investigated the impact of PA on the incidence or progression of AMD in the general population by conducting a meta-analysis of longitudinal cohort studies of the E3 – consortium. We included a total of 14,630 adults with no or early AMD at baseline from seven population-based studies and examined associations of PA with AMD incidence and progression using multi-state models per study and subsequent random effects meta-analysis. Age effects were assessed using meta-regression.

At baseline, mean age of included participants ranged from 60.7± 6.9 to 76.4 ± 4.3 years and prevalence of early AMD was 7.7%, ranging from 3.6 to 16.9% between cohorts. During follow-up, 1461 and 189 events occurred for early and late AMD, respectively. In meta-analyses, no or low to moderate PA (high PA as reference) was associated with an increased risk for incident early AMD (Hazard ratio (HR) 1.19; 95%CI=[1.01, 1.40]; p=0.04), but not for late AMD. In subsequent meta-regression, we found no association of age with the effect of PA on incident AMD.

Our study suggests that high levels of PA are protective for the development of early AMD across several population-based cohort studies. Our results establish PA as a modifiable risk factor for AMD and suggest to include PA recommendations in further AMD prevention strategies to reduce its public health impact.

Physical Activity, Incidence, and Progression of Age-Related Macular Degeneration: A Multicohort Study

MATTHIAS M. MAUSCHITZ, MARIE-THERESE SCHMITZ, TIMO VERZIJDEN, MATTHIAS SCHMID, ERIC F. THEE, JOHANNA M. COLIJN, CÉCILE DELCOURT, AUDREY COUGNARD-GRÉGOIRE, BÉNÉDICTE M.J. MERLE, JEAN-FRANÇOIS KOROBELNIK, BAMINI GOPINATH, PAUL MITCHELL, HISHAM ELBAZ, ALEXANDER K. SCHUSTER, PHILIPP S. WILD, CAROLINE BRANDL, KLAUS J. STARK, IRIS M. HEID, FELIX GÜNTHER, ANNETTE PETERS, CAROLINE C.W. KLAVER, AND ROBERT P. FINGER, ON BEHALF OF THE EUROPEAN EYE EPIDEMIOLOGY (E3) CONSORTIUM

• PURPOSE: To investigate the impact of physical activity (PA) on the incidence or progression of age-related macular degeneration (AMD) in the general population.
• DESIGN: Meta-analysis of longitudinal cohort studies.
• METHODS: We included 14,630 adults with no or early AMD at baseline from 7 population-based studies and examined associations of PA with AMD incidence and progression using multistate models (MSM) per study and subsequent random effects meta-analysis. Age effects were assessed using meta-regression. The main outcome measure was the hazard ratio (HR) for incident early or progression to late AMD.
• RESULTS: At baseline, mean age was 60.7 ± 6.9 to 76.4 ± 4.3 years, and prevalence of early AMD was 7.7% (range, 3.6%-16.9%) between cohorts. During follow-up, 1461 and 189 events occurred for early and late AMD, respectively. In meta-analyses, no or low to moderate PA (high PA as reference) was associated with an increased risk for incident early AMD (HR, 1.19; 95% CI, 1.01-1.40; $P = .04$), but not for late AMD. In subsequent meta-regression, we found no association of age with the effect of PA on incident AMD.
• CONCLUSIONS: Our study suggests high levels of PA to be protective for the development of early AMD across several population-based cohort studies. Our results establish PA as a modifiable risk factor for AMD and inform further AMD prevention strategies to reduce its public health impact. (Am J Ophthalmol 2022;236: 99–106.
© 2021 Elsevier Inc. All rights reserved.)

AJO.com Supplemental Material available at AJO.com.

Accepted for publication October 8, 2021.

Department of Ophthalmology (M.M.M., R.P.F.), University Hospital Bonn, Bonn, Germany; Department of Medical Biometry, Informatics and Epidemiology (M.-T.S., M.S.), Medical Faculty, University of Bonn, Bonn, Germany; Department of Ophthalmology (T.V., E.F.T., J.M.C., C.C.W.K.), Erasmus MC, Rotterdam, the Netherlands; Department of Epidemiology (T.V., M.S., E.F.T., J.M.C., C.C.W.K.), Erasmus MC, Rotterdam, the Netherlands; Bordeaux Population Health Research Center (C.D., A.C.-G., B.M.J.M., J.-F.K.), University of Bordeaux, Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche 1219, Team Lifelong Exposures Health and Aging (LEHA), Bordeaux, France; Centre for Vision Research, Department of Ophthalmology (B.G., P.M.), The Westmead Institute for Medical Research, The University of Sydney, Sydney, New South Wales, Australia; Department of Linguistics (B.G.,), Macquarie University Hearing, Macquarie University, Sydney, New South Wales, Australia; Department of Ophthalmology (H.E., A.K.S.), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; Department of Ophthalmology (H.E.), Otto-von-Guericke University, Magdeburg, Germany; Preventive Cardiology and Preventive Medicine, Center for Cardiology (P.S.W.), University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany; Center for Thrombosis and Hemostasis (P.S.W.), University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany; DZHK (German Center for Cardiovascular Research) (P.S.W.), partner site Rhine-Main, Mainz, Germany; Department of Genetic Epidemiology (C.B., K.J.S., I.M.H., F.G.), University Hospital Regensburg, Regensburg, Germany; Department of Ophthalmology (C.B.), University Hospital Regensburg, Regensburg, Germany; Statistical Consulting Unit StaBLab, Department of Statistics (F.G.), Ludwig-Maximilians-University Munich, Germany; Institute of Epidemiology (A.P.), Helmholtz Center Munich, Germany; Department of Epidemiology, Institute for Medical Information Processing, Biometry and Epidemiology (A.P.), Medical Faculty, Ludwig-Maximilians-Universität München, Munich, Germany; Department of Opthalmology (C.C.W.K.), Radboudumc, Nijmegen, the Netherlands; Institute of Molecular and Clinical Ophthalmology (C.C.W.K.), Basel, Switzerland

Corresponding author: Inquiries to Matthias M. Mauschitz, Department of Ophthalmology, University Hospital Bonn, Ernst-Abbe-Straße 2, 53127 Bonn, Germany; e-mail: Matthias.Mauschitz@ukbonn.de

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2021.10.008

Age-related macular degeneration (AMD) affects up to 25% of the population aged ≥55 years, and its late stage is the main cause for severe visual impairment and blindness in all high-income countries.[1–3] Late AMD causes a substantial decrease in patients' quality of life, and its economic impact was reported to be $24.4 billion per year in the United States and €89.5 billion per year in the European Union.[4,5] Over and above this impact, AMD has been associated with an increased overall and cardiovascular mortality in population-based studies.[6] Owing to current demographic trends, AMD prevalence is projected to increase by 15% and incidence by 75% until 2050.[7]

Despite the identification of several risk genes and more than 4 decades of research into AMD, we still have no specific evidence-based therapeutic intervention to prevent AMD onset or delay progression. Thus, the management

© 2021 Elsevier Inc. All rights reserved..

of lifestyle risk factors remains paramount.[8–10] Smoking conveys a 2- to 4-fold increased risk,[11] and adhering to a Mediterranean diet was reported to reduce the risk of incident late AMD by 41%.[12] Other lifestyle factors, including physical activity (PA), have been less consistently shown to alter AMD risk in often small to moderately sized studies with conflicting results.[8,13–21] However, because PA is a modifiable risk factor and because we rely on the management of modifiable risk factors in preventing onset and reducing progression of AMD, we meta-analyzed several population-based cohort studies to better characterize the effect of PA on AMD onset and progression.

METHODS

• **INCLUDED STUDIES:** We included data from the Blue Mountain Eye Study (BMES), a population study of persons aged ≥49 years residing in the Blue Mountains region in Australia[22] as well as from the European Eye Epidemiology (E3) consortium. The E3 consortium is a collaborative network across Europe with the overarching aim of developing and analyzing large data sets to increase understanding of eye diseases and vision loss.[23] For this study, we analyzed longitudinal data on PA and AMD of 14,630 participants from 7 different studies from Australia, Germany, France, and the Netherlands. We included all population-based E3 studies with available longitudinal data on PA and AMD; namely, the Rotterdam Study (RS) cohorts I-III, the POLA (Pathologies Oculaires Liées à l'Age) study, the Alienor (Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires) study, the Gutenberg-Health study (GHS), the AugUR (Age-related diseases: understanding genetic and non-genetic influences-a study at the University of Regensburg) study, and the KORA (Cooperative Health Research in the Augsburg Region) study. Data from RS I-III, POLA, and Alienor were harmonized in advance as described previously.[24] Given that the outcome was an age-related disease, we excluded participants aged <50 years in the GHS. All studies adhered to the tenets of the Declaration of Helsinki and had local ethical committee approval. All participants gave written informed consent.

• **ASSESSMENT OF AMD:** AMD was graded on color fundus photographs according to the Wisconsin age-related maculopathy grading system (WARMGS).[25] The worse eye determined the overall AMD status using the Rotterdam Classification[26] in the RS I-III studies, POLA study, Alienor study, and Gutenberg Health Study (GHS). Moreover, AMD was determined using the International Age-Related Maculopathy Epidemiological Study (IARMES) classification[26,27] in the BMES and the Beckmann initiative clinical classification of AMD in the KORA and AugUR Study.[28] The classification of late AMD (geographic atrophy and neovascular AMD) was consistent across all studies, whereas the definition of early and intermediate AMD differed between studies. To overcome these differences, all non-late AMD stages were combined. After this, AMD could be categorized into the distinct stages of early and late AMD for all studies.[8]

• **ASSESSMENT OF PA:** Within the included studies, PA was assessed using standardized self-administered or interviewer-administered questionnaires with variation in the assessment of type, intensity, amount, and context of PA.[8] These questionnaires included assessments on vigorous activity or exercise (eg, carrying loads, heavy gardening) as well as moderate activities (eg, leisure-time PA, walking, cycling, and sports, among others).[8,20,29] In addition, some studies calculated metabolic equivalents from this information according to the International Physical Activity Questionnaire scoring protocol.[20,29] To overcome the variation in PA assessments between studies, individuals were classified for each study as highly active (high PA) if they fell in the highest PA category (for assessments on a continuous scale: the higher category according to median splits), and as less active (no, low to moderate PA) otherwise (details in the Supplemental Table).

• **STATISTICAL ANALYSIS:** We used Markov multistate models (MSM)[30] to describe the process in which an individual progresses over time from no to early to late AMD. As described previously, a Markov model is a general MSM in which a system switches between different states assuming certain transition probabilities. MSMs are commonly used in studies of chronic diseases, in which patients are assumed to pass through a series of discrete disease stages with one final irreversible stage (here, late AMD), from which no transition is possible. MSMs can flexibly handle censored data and different amounts of follow-up time and hence work well in the setting of this study.[30,31]

The data of each study reflected a 3-state system and transitions between the 3 states were only possible from no to early AMD and from early to late AMD. The association between PA and transition rates was evaluated and summarized using hazard ratios (HRs) with 95% CIs adjusted for sex and smoking status (never, former, and current). As additional sensitivity analyses, we adjusted for body mass index (BMI) within RS I-III, POLA, and Alienor, because it may be a confounder in the relationship between PA and AMD. All HRs were computed using individual participant data of at least 1 eye at baseline and follow-up from each individual study.

Pooled HRs comparing individuals with high PA and low/moderate PA were estimated using meta-analysis with random effects models. Between-study heterogeneity was assessed by the Cochran Q and the Higgin and Thompson I^2 and τ^2. Results are presented using forest plots. Because we found a large heterogeneity of age in between studies, which is a potential source of noise and thus may

TABLE 1. Characteristics of Included Studies

Variable	Gutenberg Health Study[a]	KORA Study	Blue Mountain Eye Study	Rotterdam Studies I-III	POLA Study	AugUR Study	Alienor Study
Years of examination	2007-2017	1999 - 2014	1992-2009	1997-2014	1995 – 2000	2013-2015	2009-2015
City, Country	Mainz, Germany	Augsburg, Germany	Blue Mountains region, Australia	Rotterdam, the Netherlands	Sète, France	Regensburg, Germany	Bordeaux, France
Participants, No.	3978	340	1821	6192	1368	620	311
Baseline age							
Mean ± SD, y	60.7 ± 6.9	61.9 ± 4.8	63.2 ± 8.0	64.9 ± 8.0	69.5 ± 6.0	76.4 ± 4.3	81.4 ± 3.7
Range, y	50-74	54-75	49-91	50-93	60-92	70-95	76-96
Women, %	47.5 (1888)	46.5 (158)	56.7 (1033)	57.5 (3563)	58.6 (802)	44.0 (273)	63.7 (198)
Smoking. % at baseline							
Never	84.7 (3370)	46.5 (158)	51.2 (933)	30.5 (1889)	61.6 (843)	56.0 (347)	66.9 (208)
Former	2.4 (96)	39.7 (135)	34.5 (628)	49.9 (3088)	30.0 (410)	38.7 (240)	28.4 (88)
Current	12.9 (512)	13.8 (47)	12.4 (226)	19.6 (1213)	8.4 (115)	5.3 (33)	4.7 (15)
AMD, % at baseline							
No	88.9 (3535)	85.3 (290)	96.4 (1755)	94.5 (5849)	94.0 (1286)	83.1 (515)	83.6 (260)
Early	11.1 (443)	14.7 (50)	3.6 (66)	5.5 (343)	6.0 (82)	16.9 (105)	16.4 (51)
PA, % at baseline							
No, low, or moderate	50.0 (1988)	77.3 (262)	46.8 (853)	47.6 (2946)	64.8 (887)	17.7 (110)	52.7 (164)
High	50.0 (1990)	22.7 (77)	53.2 (968)	52.4 (3246)	35.2 (481)	82.3 (510)	47.3 (147)
Follow-up time, mean ± SD, y	5.0 ± 0.1	13.5 ± 0.5	15.5 ± 0.6	10.8±0.6	3.0 ± 0.2	3.2 ± 0.3	4.3 ± 0.6
AMD progression							
No AMD to early AMD	121	122	351	662	115	61	29
Early AMD to late AMD	8	10	49	87	7	20	8

[a]Individuals aged <50 years were excluded in this analysis, the total Gutenberg Health Study age range is 35 to 74 years.Alienor = Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires; AMD = age-related macular degeneration; AugUR= Age-related diseases: understanding genetic and non-genetic influences - a study at the University of Regensburg; KORA = Cooperative Health Research in the Augsburg Region; PA = physical activity; POLA = Pathologies Oculaires Liées à l'Age.

cover up moderate effects, the association of age with MSM outcomes was analyzed using meta-regression. The goodness of model fit was assessed by comparing expected and observed prevalence in all states as recommended for MSMs.[31] All analyses were performed using R 4.0.2 statistical software (R Foundation for Statistical Computing, https://www.R-project.org/) with the add-on packages msm, meta, and metafor.

RESULTS

• **PARTICIPANT CHARACTERISTICS:** The mean age of participants at baseline ranged between 60.7± 6.9 years in the Gutenberg Health Study (GHS) and 81.4 ± 3.7 years in the Alienor Study, and prevalence of early AMD at baseline ranged between 3.6% in the BMES and 16.9% in the AugUR Study. Table 1 summarizes PA levels, incidence, and progression of AMD, and further population characteristics. During the follow-up period, which averaged 7 years (range, 3.0-15.5 years), 1650 progression events occurred: 1461 from no to early and 189 from early to late AMD. The results of the unadjusted and adjusted MSM for each individual study are reported in Table 2.

In the meta-analyzed adjusted MSM, low/moderate PA was associated with an increased risk of incident early AMD; that is, with progression from no AMD to early AMD (HR, 1.19; 95% CI, 1.01-1.40; $P = .04$) (Figure 1). The GHS, which was the youngest included cohort, showed the strongest association (HR, 1.74; 95% CI, 1.21-2.51). In a subsequent sensitivity analysis, we excluded the GHS and found similar, albeit nonsignificant results (HR, 1.08; 95% CI, 0.96-1.21).

In contrast, we found no association between low/moderate PA and the progression from early AMD to late AMD (HR, 1.06; 95% CI, 0.77-1.46; $P = .77$) (Figure 2). Subsequent meta-regression analysis showed no association of age with the effect of PA on incidence of early AMD ($\beta = -0.01$ per year; 95% CI, −0.04 to 0.02; $P = .57$) or late AMD ($\beta = 0.03$ per year; 95% CI, −0.04 to 0.12; $P = .38$).

When additionally adjusting the model for BMI in sensitivity analyses using the RS I-III, POLA, and Alienor data, results remained unchanged (data not shown). The Supplemental Figure presents observed and expected prevalence rates for each AMD stage from the MSM. Although rates deviate somewhat in particular in the early AMD health

TABLE 2. Results of Multistate Markov Modeling for Each Individual Study

Study	Unadjusted Hazard Ratio (95% CI)			Adjusted[a] Hazard Ratio (95% CI)		
	PA	Progression No AMD to Early AMD	Progression Early to Late AMD	PA	Progression no AMD to Early AMD	Progression Early to Late AMD
Gutenberg Health Study[b]	No/low/moderate	1.72[c] (1.19-2.48)	0.42 (0.10-1.74)	No/low/moderate	1.74[c] (1.21-2.51)	0.49 (0.13-1.88)
	High	Reference	Reference	High	Reference	Reference
KORA Study	No/low/moderate	1.44 (0.90-2.29	0.35 (0.10-1.27)	No/low/moderate	1.42 (0.89-2.26	0.34 (0.09-1.23)
	High	Reference	Reference	High	Reference	Reference
Blue Mountain Eye Study	No/low/moderate	1.20 (0.96- .50)	1.10 (0.60-2.00)	No/low/moderate	1.16 (0.93- .45)	1.13 (0.61-2.10)
	High	Reference	Reference	High	Reference	Reference
Rotterdam Studies I-III	No/low/moderate	0.98 (0.84- .15)	1.15 (0.75-1.76)	No/low/moderate	1.00 (0.85- .17)	1.21 (0.79-1.86)
	High	Reference	Reference	High	Reference	Reference
POLA Study	No/low/moderate	1.07 (0.73- .58)	3.09 (0.37-25.70)	No/low/moderate	1.05 (0.71-1.55)	2.92 (0.34-25.04)
	High	Reference	Reference	High	Reference	Reference
AugUR Study	No/low/moderate	1.06 (0.57-2.00)	0.82 (0.24-2.80)	No/low/moderate	1.05 (0.56- .98)	0.90 (0.26-3.09)
	High	Reference	Reference	High	Reference	Reference
Alienor Study	No/low/moderate	1.43 (0.67-3.02)	1.10 (0.27-4.41)	No/low/moderate	1.60 (0.69-3.69	2.45 (0.22-27.41)
	High	Reference	Reference	High	Reference	Reference

[a] Adjusted for sex and smoking status.

[b] This analysis excluded individuals aged <50 years; the total Gutenberg Health Study age range is 35 to 74 years.

[c] *P* value <.05 (statistically significant).Alienor = Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires; AugUR = Age-related diseases: understanding genetic and non-genetic influences - a study at the University of Regensburg; KORA = Cooperative Health Research in the Augsburg Region; PA = physical activity; POLA = Pathologies Oculaires Liées à l'Age; Ref = high physical activity was used as reference value.

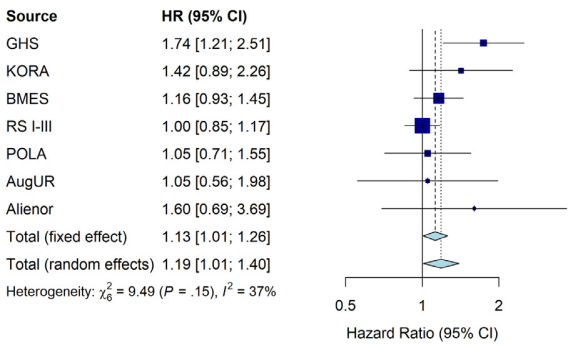

FIGURE 1. Forest plot of meta-analyzed hazard ratios (HRs) for the progression from no to early age-related macular degeneration (low/moderate physical activity vs high physical activity. The size of the box corresponds to the relative weight assigned in the pooled analysis. The horizontal lines indicate the 95% CI. The diamond denotes the weighted mean differences, and the lateral tips of the diamond indicate the associated 95% CIs. Alienor = Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires; AugUR = Age-related diseases: understanding genetic and non-genetic influences-a study at the University of Regensburg; BMES = Blue Mountain Eye Study; GHS = Gutenberg Health Study; KORA = Cooperative Health Research in the Augsburg Region; POLA = Pathologies Oculaires Liées à l'Age; RS I-III = Rotterdam Study (RS) cohorts I-III.

state, the figures indicate an acceptable fit of the overall model.

DISCUSSION

Our study indicates a protective effect of high levels of PA against the development of early AMD across a number of population-based cohort studies in White populations. We found no effect of PA on the progression from early to late AMD. Our results are in agreement with the previously reported association of low PA with higher AMD prevalence from cross-sectional studies and thus underscore the importance of PA as a modifiable lifestyle risk factor to prevent AMD.

One of the first studies on the relation between PA and prevalent AMD, a case-control study published in the early 1990s, reported an association between PA and late, but not early AMD.[32] Subsequently, various cross-sectional studies investigated the relation between PA and different stages of prevalent AMD with partly contradicting results. Whereas some studies reported increased PA to be associated with prevalent early AMD,[13,15] late AMD,[33] or any AMD,[34] other studies reported no association of AMD with physical activity.[21,35]

Subsequently, a large meta-analysis reported a positive effect of high PA on prevalent AMD.[8] The authors reported a reduction in the odds for early AMD in the physically active

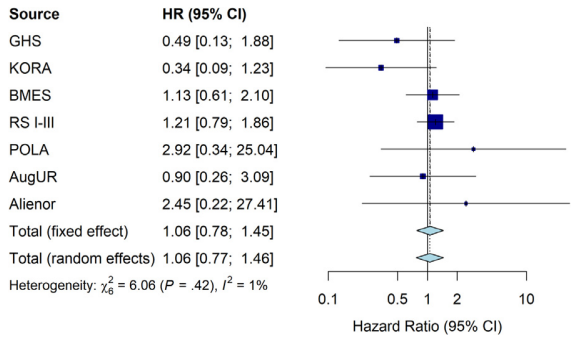

FIGURE 2. Forest plot of meta-analyzed hazard ratios (HR) for the progression from early to late age-related macular degeneration (low/moderate physical activity vs high physical activity). The size of the box corresponds to the relative weight assigned in the pooled analysis. The horizontal lines indicate the 95% CI. The diamond denotes the weighted mean differences, and the lateral tips of the diamond indicate the associated 95% CIs. Alienor = Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires; AugUR = Age-related diseases: understanding genetic and non-genetic influences-a study at the University of Regensburg; BMES = Blue Mountain Eye Study; GHS = Gutenberg Health Study; KORA = Cooperative Health Research in the Augsburg Region; POLA = Pathologies Oculaires Liées à l'Age; RS I-III = Rotterdam Study cohorts I-III.

group compared with the group with a sedentary lifestyle. This agrees with our results, which showed a larger risk for developing early AMD over time in the lower PA group. However, the authors also reported an even larger reduction of the odds for late AMD in the PA group,[8] which we cannot confirm with our longitudinal data. This is possibly due to the small number of incident late AMD cases, which led to inadequate statistical power to detect any association.

Only a few longitudinal studies have been published on the influence of PA on incident AMD. One small study reported that higher PA tended to decrease the risk for AMD progression without specifying the stage of disease.[36] Longitudinal results from the Beaver Dam Eye Study (BDES) suggest that increased PA lowers the odds for incident late AMD but not for early AMD.[14,37] In contrast, we found an association with early AMD, and again, we have likely been underpowered for the detection of any association of PA with late AMD incidence, which was at 0.9% considerably lower than the 2% in BDES. We found the strongest association of high PA on early AMD in the youngest cohort, which may indicate that the effect is largest around the sixth decade. This assumption, however, ought to be confirmed in further studies comparing younger and older cohorts.

The exact mechanisms by which PA exerts its health effects remain unclear. Regular PA was reported to increase antioxidant activity and reduce oxidative stress, which has many downstream effects, including cellular damage, altered vascular endothelial function, and increased inflammation.[38,39] The macula, with its high metabolic turnover is particularly susceptible to oxidative stress, which has been identified as a major driver in AMD pathogenesis.[11,40–42] Consequently reduced oxidative stress may contribute to the protective effect of high levels of PA on AMD progression.[8]

The strengths of this study consist of the large sample combining data of 7 studies from Europe and Australia, which represents one of the largest longitudinal studies on the association of PA on AMD incidence. AMD status was objectively assessed based on color fundus photography in all studies. Image grading protocols differed slightly between studies but were either harmonized before our analysis or used comparable classification systems. Because a meta-analysis of all participating populations was conducted, results are not limited to a single population only.

However, several limitations need to be acknowledged. Self-reported PA was not captured uniformly across studies, and rarely, the duration and intensity per session and/or context of exercise (ie, occupational, competitive sport, or leisure) was captured and accounted for. This shortcoming did not permit the accurate assessment of a dose-response relationship between accrued volume of PA and the risk of AMD. In a meta-analysis of cross-sectional studies, McGuinness and associates[8] found that a more detailed capture of self-reported PA tended to lead to larger effect sizes. Similarly, a cross-sectional study that used an accelerometer to objectively capture PA reported larger effects, in particular for late AMD.[18] Using accelerometers in future studies may allow for a much more precise quantification of PA and, thus, delineation of its effect. Unfortunately, these data are currently unavailable. The assessment of PA, similar to other lifestyle factors, is affected by social desirability and recall bias. This is likely similar across countries but may explain some of the observed heterogeneity between studies.

AMD stage may have been misclassified on a person-level due to missing data in 1 eye at one of the time points. However, previous studies reported high correlation between left and right eyes for AMD stage. In addition, including participants with data for 1 eye only has been shown to underestimate AMD prevalence in population-based studies.[43] Moreover, differences in the classification of early and preclinical stages of AMD between studies may have created noise in the data and reduced statistical power. Thus, if at all, any misclassification may have caused us to underestimate the effect of PA on AMD.

Even though we corrected our models for sex and smoking and performed a sensitivity analysis adjusting for BMI and a meta-regression assessing the impact of age, residual confounding from other risk factors, including socioeconomic status, diet, and genetics cannot be ruled out. Yet, age can be used as proxy for comorbidities in population-based studies, particularly in presence of a possible selection bias

of in general more healthy participants. Still, results ought to be interpreted with caution.

As expected, when combining different large-scale population studies, we observed between-study heterogeneity for several variables, including age and follow-up time. As described, this heterogeneity between studies was addressed by using random effect meta-analysis and subsequent meta-regression adjusting for age. Yet, residual confounding of age on the effect of PA on AMD incidence cannot be fully excluded. Given that the association was strongest in the youngest cohort around the sixth decade, we may have missed an association in younger participants and thus may have underestimated the effect of PA on early AMD incidence. The combination of potential noise within PA data, the heterogeneity between studies, and a potential selection bias of more healthy participants has likely resulted in less statistical power and contributed to the moderate effect size of our detected association.

Lastly, all of the population studies were mostly of White race/ethnicity and results may not be generalizable to other populations.

In conclusion, we found high levels of PA are associated with a reduced risk of early AMD incidence across several large population-based cohorts. Our data suggest a stronger association in the younger population and underscore the importance of PA as a modifiable lifestyle risk factor for AMD. Based on our results, we conclude lifestyle advice for patients at risk of AMD ought to include recommendations to be physically active.

Funding/Support: 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 "Wissenschafft Zukunft" and "Center for Translational Vascular Biology (CTVB)" of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim and Philips Medical Systems, including an unrestricted grant for the Gutenberg Health Study. Funders were involved in the development of the study design as scientific consultants. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Philipp S. Wild is funded by the Federal Ministry of Education and Research (BMBF 01EO1503) and is the principle investigator of the German Center for Cardiovascular Research (DZHK). Alexander K. Schuster holds the professorship for ophthalmic health care research endowed by "Stiftung Auge" and financed by "Deutsche Ophthalmologische Gesellschaft" and "Berufsverband der Augenärzte Deutschland e.V." The Alienor study was supported by Théa Pharma, Fondation Voir et Entendre, Retina France, Agence Nationale de la Recherche (ANR 2010-PRSP-011 VISA), CFSR Recherche (Club Francophone des Spécialistes de la Rétine), French Ministry of Health (PHRC, 2012, PHRC12_157 ECLAIR), and CNSA (Caisse Nationale pour la Solidarité et l'Autonomie). The POLA 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. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the 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), and the Municipality of Rotterdam. Supported by the European Union Horizon 2020 grant No. 634479 (EYE-RISK) and Royal Dutch Academy of Sciences (Ammodo Award to Caroline C.W. Klaver). AugUR investigations and analyses are supported by grants from the German Federal Ministry of Education and Research (BMBF 01ER1206, BMBF 01ER1507 to Iris M. Heid) and by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation; HE 3690/7-1 to I.M.H., BR 6028/2-1 to Caroline Brandl). The Blue Mountains Eye Study was funded by the Australian National Health and Medical Research Council (Grant Nos. 974159, 991407, 211069, 262120, and 457349). Matthias Schmid received funding paid to the institution from Innovative Medicines Initiative (MACUSTAR project).
Financial Disclosures: Alexander K. Schuster discloses research support from Allergan, Bayer Vital, and Novartis and receipt of equipment from PlusOptix, Heidelberg Engineering. Jean-Francois Korobelnik discloses consulting fees from Allergan-AbbVie, Bayer, Janssen, Kanghong, NanoRetina, Novartis, Novonordisk, Roche, Laboratoires Théa, and Carl Zeiss Meditec. Audrey Cougnard-Gregoire discloses travel fees from Laboratoires Théa. Cécile Delcourt discloses consulting fees from Allergan, Bausch and Lomb, Laboratoires Théa, and Novartis. Matthias Schmid discloses support for attending meetings and/or travel from Innovative Medicines Initiative and European Federation of Pharmaceutical Industries and Associations (as part of MACUSTAR activities) paid to his institution. Philipp S. Wild discloses grants and personal fees from Boehringer Ingelheim, Sanofi-Aventis, Bayer Health Care, Bayer Vital, Daiichy Sankyo, and Novartis Pharma; grants from Philips Medical Systems and Novartis Pharma; provision of laboratory assays from DiaSorin; and personal fees from AstraZeneca. Caroline Klaver discloses fees in connection with advisory board for Bayer and is a member of the European Society for Retinal Specialists Board. Robert Finger reports grants and personal fees from Novartis, and personal fees from Bayer, Santen, Opthea, Novelion, ProQR, Oxford Innovation, Roche, Alimera, Santhera, Inositec, and Ellex, outside the submitted work. The other authors indicate no financial support or conflicts of interest. All authors attest that they meet the current ICMJE criteria for authorship.
Acknowledgments: The authors are grateful to the study participants, the staff from the Rotterdam Study, and the participating general practitioners and pharmacists.

REFERENCES

1. Finger RP, Fimmers R, Holz FG, Scholl HPN. Prevalence and causes of registered blindness in the largest federal state of germany. *Br J Ophthalmol*. 2011;95(8):1061–1067. doi:10.1136/bjo.2010.194712.
2. Klein R, Klein BEK. The prevalence of age-related eye diseases and visual impairment in aging: current estimates. *Invest Ophthalmol Vis Sci*. 2013;54(14):ORSF5–ORSF13. doi:10.1167/iovs.13-12789.
3. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. *Lancet*. 2018;392(10153):1147–1159. doi:10.1016/S0140-6736(18)31550-2.
4. Brown GC, Brown MM, Sharma S, et al. The burden of age-related macular degeneration: a value-based medicine analysis. *Trans Am Ophthalmol Soc*. 2005;103:173–184 [discussion 184-186]..
5. Jaki Mekjavić P, Jūratė Balčiūnienė V, Ćeklić L, et al. The burden of macular diseases in central and eastern europe-implications for healthcare systems. *Value Health Reg Issues*. 2019;19:1–6. doi:10.1016/j.vhri.2018.11.002.

6. McGuinness MB, Karahalios A, Finger RP, Guymer RH, Simpson JA. Age-related macular degeneration and mortality: a systematic review and meta-analysis. *Ophthalmic Epidemiol.* 2017;24(3):141–152. doi:10.1080/09286586.2016.1259422.
7. Li JQ, Welchowski T, Schmid M, Mauschitz MM, Holz FG, Finger RP. Prevalence and incidence of age-related macular degeneration in europe: a systematic review and meta-analysis. *Br J Ophthalmol.* 2020;104(8):1077–1084. doi:10.1136/bjophthalmol-2019-314422.
8. McGuinness MB, Le J, Mitchell P, et al. Physical activity and age-related macular degeneration: a systematic literature review and meta-analysis. *Am J Ophthalmol.* 2017;180:29–38. doi:10.1016/j.ajo.2017.05.016.
9. Colijn JM, Meester M, Verzijden T, et al. Genetic risk, lifestyle, and amd in europe: the eye-risk consortium. *Ophthalmology.* 2021;128(7):1039–1049. doi:10.1016/j.ophtha.2020.11.024.
10. Colijn JM, den Hollander AI, Demirkan A, et al. Increased high-density lipoprotein levels associated with age-related macular degeneration: evidence from the eye-risk and european eye epidemiology consortia. *Ophthalmology.* 2019;126(3):393–406. doi:10.1016/j.ophtha.2018.09.045.
11. Heesterbeek TJ, Lorés-Motta L, Hoyng CB, Lechanteur YTE. Hollander ai den. risk factors for progression of age-related macular degeneration. *Ophthalmic Physiol Opt.* 2020;40(2):140–170. doi:10.1111/opo.12675.
12. Merle BMJ, Colijn JM, Cougnard-Grégoire A, et al. Mediterranean diet and incidence of advanced age-related macular degeneration: the eye-risk consortium. *Ophthalmology.* 2019;126(3):381–390. doi:10.1016/j.ophtha.2018.08.006.
13. Mares JA, Voland RP, Sondel SA, et al. Healthy lifestyles related to subsequent prevalence of age-related macular degeneration. *Arch Ophthalmol.* 2011;129(4):470–480. doi:10.1001/archophthalmol.2010.314.
14. Knudtson MD, Klein R, Klein BEK. Physical activity and the 15-year cumulative incidence of age-related macular degeneration: the beaver dam eye study. *Br J Ophthalmol.* 2006;90(12):1461–1463. doi:10.1136/bjo.2006.103796.
15. Munch IC, Linneberg A, Larsen M. Precursors of age-related macular degeneration: associations with physical activity, obesity, and serum lipids in the inter99 eye study. *Invest Ophthalmol Vis Sci.* 2013;54(6):3932–3940. doi:10.1167/iovs.12-10785.
16. McGuinness MB, Finger RP, Karahalios A, et al. Age-related macular degeneration and mortality: the melbourne collaborative cohort study. eye (Lond). 2017;31(9):1345-1357. doi:10.1038/eye.2017.139
17. Heinemann M, Welker SG, Li JQ, et al. Impact of visual impairment on physical activity in early and late age-related macular degeneration. *PLoS One.* 2019;14(10):e0222045. doi:10.1371/journal.pone.0222045.
18. Loprinzi PD, Swenor BK, Ramulu PY. Age-related macular degeneration is associated with less physical activity among us adults: cross-sectional study. *PLoS One.* 2015;10(5):e0125394. doi:10.1371/journal.pone.0125394.
19. McGuinness MB, Karahalios A, Simpson JA, et al. Past physical activity and age-related macular degeneration: the melbourne collaborative cohort study. *Br J Ophthalmol.* 2016;100(10):1353–1358. doi:10.1136/bjophthalmol-2015-307663.
20. Gopinath B, Liew G, Burlutsky G, Mitchell P. Physical activity and the 15-year incidence of age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2014;55(12):7799–7803. doi:10.1167/iovs.14-15575.
21. Klein R, Cruickshanks KJ, Nash SD, et al. The prevalence of age-related macular degeneration and associated risk factors. *Arch Ophthalmol.* 2010;128(6):750–758. doi:10.1001/archophthalmol.2010.92.
22. Joachim N, Mitchell P, Burlutsky G, Kifley A, Wang JJ. The incidence and progression of age-related macular degeneration over 15 years: the blue mountains eye study. *Ophthalmology.* 2015;122(12):2482–2489. doi:10.1016/j.ophtha.2015.08.002.
23. Delcourt C, Korobelnik J-F, Buitendijk GHS, et al. Ophthalmic epidemiology in europe: the "European eye epidemiology" (E3) consortium. *Eur J Epidemiol.* 2016;31(2):197–210. doi:10.1007/s10654-015-0098-2.
24. Colijn JM, Buitendijk GHS, Prokofyeva E, et al. Prevalence of age-related macular degeneration in europe: the past and the future. *Ophthalmology.* 2017;124(12):1753–1763. doi:10.1016/j.ophtha.2017.05.035.
25. Wang JJ, Rochtchina E, Lee AJ, et al. Ten-year incidence and progression of age-related maculopathy: the blue mountains eye study. *Ophthalmology.* 2007;114(1):92–98. doi:10.1016/j.ophtha.2006.07.017.
26. Thee EF, Meester-Smoor MA, Luttikhuizen DT, et al. Performance of classification systems for age-related macular degeneration in the rotterdam study. *Transl Vis Sci Technol.* 2020;9(2):26. doi:10.1167/tvst.9.2.26.
27. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. the international arm epidemiological study group. *Surv Ophthalmol.* 1995;39(5):367–374. doi:10.1016/s0039-6257(05)80092-x.
28. Ferris FL, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. *Ophthalmology.* 2013;120(4):844–851. doi:10.1016/j.ophtha.2012.10.036.
29. Albrecht M, Koolhaas CM, Schoufour JD, et al. Physical activity types and atrial fibrillation risk in the middle-aged and elderly: the rotterdam study. *Eur J Prev Cardiol.* 2018;25(12):1316–1323. doi:10.1177/2047487318780031.
30. Petiot V, Quantin C, Le Teuff G, et al. Disability evolution in multiple sclerosis: how to deal with missing transition times in the markov model? *Neuroepidemiology.* 2007;28(1):56–64. doi:10.1159/000098518.
31. Finger RP, Puth M-T, Schmid M, Barthelmes D, Guymer RH, Gillies M. Lifetime outcomes of anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration. *JAMA Ophthalmol.* 2020;138(12):1234–1240. doi:10.1001/jamaophthalmol.2020.3989.
32. Risk factors for neovascular age-related macular degeneration. the eye disease case-control study group. *Arch Ophthalmol.* 1992;110(12):1701–1708. doi:10.1001/archopht.1992.01080240041025.
33. Erke MG, Bertelsen G, Peto T, Sjølie AK, Lindekleiv H, Njølstad I. Cardiovascular risk factors associated with age-related macular degeneration: the tromsø study. *Acta Ophthalmol.* 2014;92(7):662–669. doi:10.1111/aos.12346.

34. Saksens NTM, Kersten E, Groenewoud JMM, et al. Clinical characteristics of familial and sporadic age-related macular degeneration: differences and similarities. *Invest Ophthalmol Vis Sci*. 2014;55(11):7085–7092. doi:10.1167/iovs.14-14659.
35. Nidhi B, Mamatha BS, Padmaprabhu CA, Pallavi P, Vallikannan B. Dietary and lifestyle risk factors associated with age-related macular degeneration: a hospital based study. *Indian J Ophthalmol*. 2013;61(12):722–727. doi:10.4103/0301-4738.120218.
36. Seddon JM, Cote J, Davis N, Rosner B. Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist-hip ratio. *Arch Ophthalmol*. 2003;121(6):785–792. doi:10.1001/archopht.121.6.785.
37. Klein R, Klein BEK, Tomany SC, Cruickshanks KJ. The association of cardiovascular disease with the long-term incidence of age-related maculopathy: the beaver dam eye study. *Ophthalmology*. 2003;110(6):1273–1280. doi:10.1016/S0161-6420(03)00599-2.
38. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? *Free Radic Biol Med*. 2010;49(11):1603–1616. doi:10.1016/j.freeradbiomed.2010.09.006.
39. Mury P, Chirico EN, Mura M, Millon A, Canet-Soulas E, Pialoux V. Oxidative stress and inflammation, key targets of atherosclerotic plaque progression and vulnerability: potential impact of physical activity. *Sports Med*. 2018;48(12):2725–2741. doi:10.1007/s40279-018-0996-z.
40. Khandhadia S, Lotery A. Oxidation and age-related macular degeneration: insights from molecular biology. *Expert Rev Mol Med*. 2010;12:e34. doi:10.1017/S146239941000164X.
41. Bloomer RJ, Fisher-Wellman KH. Blood oxidative stress biomarkers: influence of sex, exercise training status, and dietary intake. *Gend Med*. 2008;5(3):218–228. doi:10.1016/j.genm.2008.07.002.
42. Kersten E, Paun CC, Schellevis RL, et al. Systemic and ocular fluid compounds as potential biomarkers in age-related macular degeneration. *Surv Ophthalmol*. 2018;63(1):9–39. doi:10.1016/j.survophthal.2017.05.003.
43. Brandl C, Zimmermann ME, Günther F, et al. On the impact of different approaches to classify age-related macular degeneration: results from the german augur study. *Sci Rep*. 2018;8(1):8675. doi:10.1038/s41598-018-26629-5.

Mauschitz MM, Verzijden T, Schuster AK, Elbaz H, Pfeiffer N, Khawaja A, Luben RN, Foster PJ, Rauscher FG, Wirkner K, Kirsten T, Jonas JB, Bikbov MM, Hogg R, Peto T, Cougnard-Grégoire A, Bertelsen G, Erke MG, Topouzis F, Giannoulis DA, Brandl C, Heid IM, Creuzot-Garcher CP, Gabrielle PH, Hense HW, Pauleikhoff D, Barreto P, Coimbra R, Piermarocchi S, Daien V, Holz FG, Delcourt C, Finger RP; European Eye Epidemiology (E3) Consortium. **Association of lipid-lowering drugs and antidiabetic drugs with age-related macular degeneration: a meta-analysis in Europeans.** Br J Ophthalmol.2023 Nov 22;107(12):1880-1886. DOI: 10.1136/bjo-2022-321985

In this study, we investigated the association of commonly used systemic medications with prevalent AMD in the general population by performing a meta-analysis of 14 population- and hospital-based studies from the E3 – consortium. We examined associations between the use of systemic medications and any prevalent AMD as well as any late AMD using multivariable logistic regression modelling per study and pooled results using random effects meta-analysis.

Among studies, mean age of the 38,694 included adults ranged from 61.5 ± 7.1 to 82.6 ± 3.8 years and prevalence ranged from 12.1% to 64.5% and from 0.5% to 35.5% for any and late AMD, respectively. In the meta-analysis, lipid-lowering and antidiabetic drugs were associated with lower prevalence of any AMD (Odds ratio (OR) 0.85, 95% confidence interval (CI)=0.79 - 0.91 and OR 0.78, 95% CI=0.66 - 0.91). We found no association with late AMD or with any other medication.

Our study indicates a potential beneficial effect of LLD and antidiabetic drug use on prevalence of AMD across multiple European cohorts. Our findings support the importance of metabolic processes in the multifactorial etiology of AMD and ought to be confirmed using longitudinal data.

Association of lipid-lowering drugs and antidiabetic drugs with age-related macular degeneration: a meta-analysis in Europeans

Matthias M Mauschitz ,[1] Timo Verzijden,[2,3] Alexander K Schuster,[4] Hisham Elbaz,[4] Norbert Pfeiffer,[4] Anthony Khawaja,[5,6] Robert N Luben,[5,6] Paul J Foster ,[5] Franziska G Rauscher,[7,8] Kerstin Wirkner,[7,8] Toralf Kirsten,[7,8,9] Jost B Jonas ,[10,11] Mukharram M Bikbov,[12] Ruth Hogg ,[13] Tunde Peto ,[5,13] Audrey Cougnard-Grégoire,[14] Geir Bertelsen,[15,16] Maja Gran Erke ,[17,18] Fotis Topouzis,[19] Dimitrios A Giannoulis ,[19] Caroline Brandl,[20,21] Iris M Heid,[20] Catherine P Creuzot-Garcher,[22] Pierre-Henry Gabrielle ,[22] Hans-Werner Hense,[23] Daniel Pauleikhoff,[24] Patricia Barreto,[25,26,27] Rita Coimbra,[25] Stefano Piermarocchi,[28,29] Vincent Daien ,[30,31,32] Frank G Holz,[1] Cecile Delcourt ,[14] Robert P Finger,[1] On behalf of the European Eye Epidemiology (E3) Consortium

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjo-2022-321985).

For numbered affiliations see end of article.

Correspondence to
Dr Matthias M Mauschitz, Department of Ophthalmology, University Hospital Bonn, Bonn, Germany;
matthias.mauschitz@ukbonn.de

Received 22 June 2022
Accepted 27 September 2022

Check for updates

© Author(s) (or their employer(s)) 2022. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Mauschitz MM, Verzijden T, Schuster AK, *et al*. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjo-2022-321985

ABSTRACT

Background/aims To investigate the association of commonly used systemic medications with prevalent age-related macular degeneration (AMD) in the general population.

Methods We included 38 694 adults from 14 population-based and hospital-based studies from the European Eye Epidemiology consortium. We examined associations between the use of systemic medications and any prevalent AMD as well as any late AMD using multivariable logistic regression modelling per study and pooled results using random effects meta-analysis.

Results Between studies, mean age ranged from 61.5±7.1 to 82.6±3.8 years and prevalence ranged from 12.1% to 64.5% and from 0.5% to 35.5% for any and late AMD, respectively. In the meta-analysis of fully adjusted multivariable models, lipid-lowering drugs (LLD) and antidiabetic drugs were associated with lower prevalent any AMD (OR 0.85, 95% CI=0.79 to 0.91 and OR 0.78, 95% CI=0.66 to 0.91). We found no association with late AMD or with any other medication.

Conclusion Our study indicates a potential beneficial effect of LLD and antidiabetic drug use on prevalence of AMD across multiple European cohorts. Our findings support the importance of metabolic processes in the multifactorial aetiology of AMD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies suggested an association of the use of specific systemic medication with age-related macular degeneration (AMD) prevalence. Yet, these studies were often based on small and mainly clinical cohorts and reported partly contradicting results.

WHAT THIS STUDY ADDS

⇒ This is the first large-scale study showing an association of using lipid-lowering drugs and antidiabetic drugs with lower AMD prevalence in the general population using data from multiple European cohort studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings have implications for public health messages, underline the link of AMD with cardiovascular comorbidities and may provide potential future therapeutic targets.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause for severe visual impairment and blindness in high-income countries and particularly affects the population above the age of 55 years.[1 2] In Europe, 67 million people are currently affected by AMD and prevalence is projected to increase by 15% and incidence by 75% until the year 2050 due to population ageing.[3]

AMD is a complex multifactorial disease with genetic and environmental risk factors associated with ageing.[4–7] Beside lifestyle risk factors such as smoking and sedentary lifestyle, chronic inflammation and increased oxidative stress have been discussed as pathoetiogenetic drivers.[6 8–10]

The retina is a metabolically highly active tissue with a large turnover of lipids and proteins and several metabolites have been associated with AMD occurrence.[11 12] Resulting degradation products lead to the formation of drusen, which represent a hallmark AMD lesion and contain oxidated debris of lipids and proteins.[9 13 14]

Despite decades of research, we still lack therapeutic measures and interventions to prevent AMD or slow down progression,[10 12 15] underscoring the need for better understanding and novel prevention or therapeutic strategies. Previous studies

Table 1 Characteristic of included studies

Study		n	Age (mean±SD)	Women (%)	AMD (%)						Systemic use (%)			
					No		Early		Late					
					n	%	n	%	n	%	NSAID	LLD	Antidiabetics	L-Dopa
EYERISK*	Tromsø[P]	*3025*	72.5±5.4	57.6%	2298	76.0%	635	21.0%	92	3.0%	NA	28.5%	6.3%	NA
	Thessaloniki[P]	*2629*	71.4±6.4	47.5%	2106	80.1%	462	17.6%	61	2.3%	NA	NA	12.2%	NA
	Montrachet[P]	*1153*	82.3±3.8	62.7%	910	78.9%	219	19.0%	24	2.1%	NA	41.7%	NA	NA
	MARS[C]	*970*	70.9±5.5	60.5%	344	35.5%	282	29.0%	344	35.5%	33.1%	30.6%	13.5	NA
	Alienor[P]	*963*	80.2±4.5	61.9%	769	79.9%	148	15.4%	46	4.7%	7.8%	40.1%	10.3%	NA
	PAMDI[P]	*855*	71.5±7.0	54.2%	722	84.4%	115	13.5%	18	2.1%	10.5%	44.3%	32.8%	NA
	Crescendo-3C[P]	*380*	82.6±3.8	55.5%	302	79.4%	61	16.1%	17	4.5%	6.6%	42.0%	8.4%	NA
GHS*[P]		7946	61.5±7.1	49.7%	6983	87.9%	914	11.5%	49	0.6%	34.9%	18.9%	8.5%	0.6%
EPIC-Norfolk[P]		5418	67.0±8.0	57.0%	4202	77.6%	1187	21.9%	29	0.5%	8.0%	22.0%	3.7%	0.5%
LIFE-Adult*[P]		4808	63.4±8.0	52.9%	2948	61.3%	1860	38.7%	NA	NA	15.0%	16.8%	10.6%	0.6%
UEMS[P]		4030	62.4±8.7	60.5%	3465	86.0%	520	12.9%	45	1.1%	14.1%	10.3%	7.9%	NA
NICOLA[P]		3265	63.5±8.9	52.3%	2590	79.3%	649	19.9%	26	0.8%	7.1%	31.9%	5.6%	0.5%
AugUR[P]		2304	77.8±5.0	52.6%	1124	48.8%	1005	43.6%	175	7.6%	12.6%	34.8%	15.8%	2.5%
CES[P]		948	72.3±6.8	58.2%	599	63.2%	324	34.2%	25	2.6%	6.4%	44.6%	18.2%	0.8%

Superscript P indicates population-based study and superscript C indicates case–control study.
Characteristics based on participants with available data on AMD, age and sex and at least one medication; sample size of model 2 is smaller due to missing data on covariables.
*Participants below the age of 50 years were excluded in this analysis.
Alienor, Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires; AMD, age-related macular degeneration; AugUR, Age-related diseases: understanding genetic and non-genetic influences—a study at the University of Regensburg; CES, Coimbra Eye Study; Crescendo-3C, Crescendo-3C Study; EPIC-Norfolk, European Prospective Investigation into Cancer and Nutrition in Norfolk; GHS, Gutenberg Health Study; LIFE-Adult, (Leipzig Research Centre for Civilization Diseases)—Adult Study; LLD, lipid-lowering drugs; MARS, Muenster Ageing and Retina Study; Montrachet, Montrachet Study; NICOLA, Northern Ireland Cohort for the Longitudinal Study of Ageing; NSAID, non-steroidal anti-inflammatory drugs; PAMDI, Prevalence of Age-Related Macular Degeneration in Italy Study; Thessaloniki, Thessaloniki Eye Study; Tromsø, Tromsø Eye Study; UEMS, Ural Eye and Medical Study.

investigated the relation of AMD and different systemic medications, which interfere with pathways that also play a role in AMD pathogenesis and hence may affect it. These include lipid-lowering drugs (LLD)[16] for the lipid metabolism and lipid accumulation, non-steroidal anti-inflammatory drugs (NSAID)[17–19] and antidiabetic drugs (particularly metformin),[20 21] which may reduce inflammation and oxidative stress, and levodopa (L-Dopa),[22] which was reported to upregulate the retinal pigment epithelium (RPE) metabolism. Metformin and LLD rank among the top prescribed drugs in Germany, Europe and the USA,[23 24] while NSAID are some of the most frequently used over-the-counter (OTC) drugs.[25] Results of studies to date, however, have been inconsistent, based on small sample size or used self-reported AMD as outcome.[16 26–32] Thus, it remains unclear as to whether any of these drugs are associated with AMD.

Hence, we aimed to explore associations between the use of aforementioned medications and presence of AMD in the European Eye Epidemiology (E3) population.

METHODS

Included studies

The E3 consortium is a collaborative network across Europe with the overarching aim of developing and analysing large pooled datasets to increase understanding of eye diseases and vision loss.[33] For this meta-analysis, we included 14 population or hospital-based E3 studies with available data on systemic medication use and AMD from France, Germany, Greece, Ireland, Italy, Norway, Portugal, Russia and the UK (table 1). Data from seven included studies from the EYERISK project (Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires—Study (Alienor), Crescendo-3C Study, Muenster Aging and Retina Study (MARS), Montrachet Study, Prevalence of Age-Related Macular Degeneration in Italy—Study, Thessaloniki Eye Study and Tromsø Eye Study) were harmonised in advance as described previously.[7]

The other seven included studies were the Age-related diseases: understanding genetic and non-genetic influences—a study at the University of Regensburg—Study (AugUR),[34] the Coimbra Eye Study (CES),[35] the European Prospective Investigation into Cancer–Norfolk—Study (EPIC-Norfolk),[36] the Gutenberg Health Study (GHS),[37] the Leipzig Research Centre for Civilization Diseases (LIFE)—Adult Study (LIFE-Adult),[38] the Northern Ireland Cohort for the Longitudinal Study of Ageing—Study (NICOLA)[39] and the Ural Eye and Medical Study (UEMS).[40] Given that the outcome was AMD, we excluded participants below the age of 50. All studies adhered to the tenets of the Declaration of Helsinki and had local ethical committee approval. All participants gave written informed consent.

Grading of AMD

AMD was graded on colour fundus photographs according to the Wisconsin age-related maculopathy grading system (WARMGS).[41] The worse eye determined the overall AMD status using the Rotterdam classification[42] in the EYERISK studies, the CES, the GHS and LIFE-Adult,[43] the Beckmann initiative clinical classification of AMD in AugUR, NICOLA and UEMS[44] and a modified WARMGS protocol in EPIC-Norfolk.[36]

The classification of late AMD, that is, geographic atrophy (GA) and macular neovascularisation (MNV), was consistent across all studies, whereas the definition of early and intermediate AMD differed between studies. To overcome this heterogeneity, we assessed the presence of both ‘any AMD’ and of ‘late AMD’.

Medication assessments

Medication assessments differed between studies and were either assessed in standardised questionnaires or using scanned records from drug blisters provided by the participants using the Anatomical Therapeutic Chemical (ATC) classification system. We investigated associations of LLD (ATC codes C10), antidiabetic drugs (including insulin (ATC codes A10)), NSAID (ATC codes M01A and B01AC06) and L-dopa (ATC codes N04BA), with AMD prevalence.

Statistical analysis

We performed descriptive statistics and multivariable logistic regression models with prevalent AMD as dependent variable and the respective medication as independent variable. Model 1 was controlled for age and sex and the fully adjusted model 2 was controlled for age, sex, body mass index (BMI), smoking status (never, former, current) and prevalence of hypertension and diabetes as potential confounders (models on antidiabetic drugs were not adjusted for prevalent diabetes). Covariables were chosen a priori on the basis of literature and availability in the individual studies. We conducted all models for each individual study; data from seven previously harmonised studies from EYERISK were pooled and models were additionally adjusted for study.[7]

Subsequently, we performed random effects meta-analysis to combine effect estimates presented as ORs with 95% CI of each medication from the multivariable models among studies. A random effects approach was chosen a priori on the basis of the heterogeneity of study participants and the design of the studies.[45] As further analysis, we repeated all logistic regression models with prevalent late AMD as dependent variable.

Not all studies held information on all medications or covariables and within UEMS smoking status only distinguished current smokers from non-smokers, which included former smokers. In the event that studies were unable to provide a model due to a missing exposure, that study was excluded from the respective model. Moreover, we excluded EPIC-Norfolk from all and CES, NICOLA and GHS from some models of late AMD, because there were too few cases (either of late AMD or medication use), that did not allow for robust statistical modelling. Given that the LIFE-Adult only had data on prevalence of early AMD, we repeated the meta-analysis without LIFE-Adult data as a sensitivity analysis. All analyses were performed with the statistical software RStudio (V.4.0.2, R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/) with the add-on package metafor.

RESULTS

Mean age of 38 694 participants (with available data on AMD, age, sex and at least one medication) ranged from 61.5±7.1 years in the GHS to 82.6±3.8 years in the Crescendo-3C Study. Prevalence of any AMD ranged from 12.1% in the GHS to 64.5% in MARS and prevalence of late AMD ranged from 0.5% in the EPIC-Norfolk Study to 35.5% in MARS, with 9332 and 951 cases for any and late AMD, respectively. Table 1 presents further population characteristics and use of systemic medications.

In our random effects meta-analysis, we found LLD intake and use of antidiabetic drugs to be associated with lower AMD prevalence in both the basic model 1 (online supplemental figures 1 and 2) and the fully adjusted model 2 (OR 0.85; 95% CI 0.79 to 0.91; p<0.001, I^2=0%; and OR 0.78; 95% CI 0.66 to 0.91, p=0.002, I^2=57%, respectively; figures 1 and 2). We observed

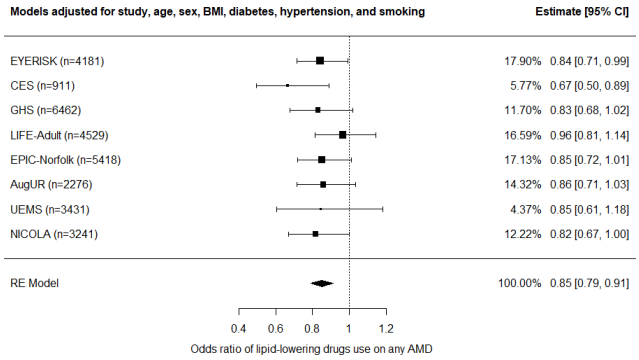

Figure 1 Forest plot of meta-analysed associations of lipid-lowering drugs with prevalent AMD (model 2; n=30 449, I^2 heterogeneity=0%). AMD, age-related macular degeneration; AugUR, Age-related diseases: understanding genetic and non-genetic influences—a study at the University of Regensburg—Study; BMI, body mass index; CES, Coimbra Eye Study; EPIC-Norfolk, European Prospective Investigation into Cancer–Norfolk—Study; GHS, Gutenberg Health Study; NICOLA, Northern Ireland Cohort for the Longitudinal Study of Ageing; RE, random-effects; UEMS, Ural Eye and Medical Study.

no association of LLD and antidiabetic drugs with late AMD (OR 0.87; 95% CI 0.71 to 1.06; p=0.16, I^2=0%; and OR 1.12; 95% CI 0.87 to 1.44, p=0.37, I^2=0%, for model 2, respectively; online supplemental figures 3 and 4) and no association of NSAID and L-dopa with any form of AMD (online supplemental figures 5–8). Additional sensitivity analyses, excluding LIFE-Adult data, showed similar results (data not shown).

DISCUSSION

Our study indicates an association of systemic use of LLD and antidiabetic drugs with lower AMD prevalence across several European cohort studies. We found no association with late AMD or further systemic medication, which is likely due to a lack of statistical power and/or potential survival bias. Our results are in agreement with previous studies and suggest a potentially positive effect of these commonly used drugs on AMD prevalence.

One of the first studies on the impact of statins on AMD used longitudinal data of 2780 participants and could not find

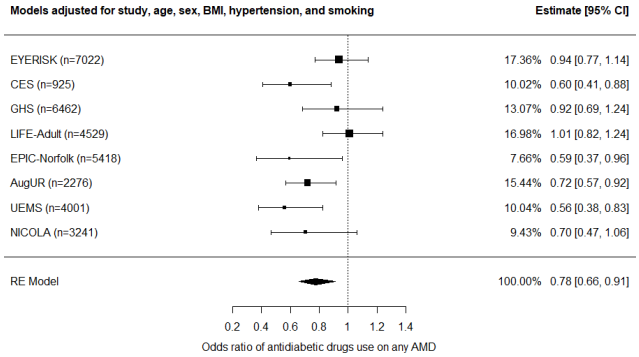

Figure 2 Forest plot of meta-analysed associations of antidiabetic drugs with prevalent AMD (model 2; n=33 874; I^2 heterogeneity=57%). AugUR, Age-related diseases: understanding genetic and non-genetic influences—a study at the University of Regensburg—Study; BMI, body mass index; CES, Coimbra Eye Study; EPIC-Norfolk, European Prospective Investigation into Cancer–Norfolk—Study; GHS, Gutenberg Health Study; NICOLA, Northern Ireland Cohort for the Longitudinal Study of Ageing; RE, random-effects; UEMS, Ural Eye and Medical Study.

an association of LLD with AMD incidence or progression.[27] Subsequently, several cross-sectional and longitudinal studies of different sample size investigated this relationship and reported inconsistent results.[46] While some studies reported possibly beneficial impact of statins on cross-sectional AMD prevalence[32] and progression over time,[26 29 47] other studies, both cross-sectional and longitudinal, did not find any associations[30 31 48–52] or even suggested an increased risk for neovascular AMD.[28] One recent review maintains the potentially beneficial role of statins in AMD while underscoring the complexity of underlying associations,[53] while two others could not confirm an association.[54 55] Our study supports the body of evidence suggesting a beneficial association with AMD and represents, to our knowledge, the first study meta-analysing individual level data from various population-based and hospital-based studies instead of meta-analysing published aggregated results only. Yet, further longitudinal data are needed to confirm our findings, which are inherently limited by using cross-sectional data only and cannot infer causality. Apart from lowering serum levels of low-density lipoprotein and cholesterol, various LLD have been reported to have anti-inflammatory and antioxidant effects, which also play a role in AMD pathogenesis.[6 9 16] However, even though the beneficial impact of LLD on AMD seems biologically plausible, support for this assertion in longitudinal studies would strengthen the evidence. Earlier randomised controlled trials (RCT) failed to show a causal relation,[48 49] likely due to the multifactorial nature of the disease, small sample size and limited follow-up. Interestingly, several studies reported an association of higher levels of high-density lipoprotein (HDL) and specific subclasses such as HDL-C with an increased risk of AMD.[12 56 57] This opposes the generally beneficial role of HDL in cardiovascular disease (CVD) and underscores the complexity and need for further intensive research. Particularly, given that statins have been reported to increase serum levels of HDL-C, which would conflict our results of an association of lower AMD prevalence in statin use.[58 59]

Lastly, while statins have a safe side effect profile, rare and serious adverse reactions such as rhabdomyolysis can occur and statin therapy needs to be monitored by physicians.[60]

Until now, the few studies investigating the impact of antidiabetic drugs, mainly metformin, on AMD were partly conflicting. Some studies reported metformin use to be associated with reduced odds of prevalent[20] or incident AMD,[21 61 62] yet others could not confirm a relationship.[51 63] Blitzer *et al* described the largest benefit of metformin at a low-to-moderate dosage, indicating a U-shaped dose–response and hypothesised that a high dose may have been indicated in patients with poorly controlled diabetes who hence may benefit less from metformin use. Subsequently, a recent meta-analysis on retrospective data suggested a trend of reduced risk for AMD in patients using metformin without reaching statistical significance, underscoring the scarcity of data and highlighting the need for further prospective studies.[64] Suggested mechanisms include different pathways of biological ageing. Metformin is considered to have antioxidative and anti-inflammatory properties and to reduce oxidative stress within the RPE, which is an important part of AMD pathophysiology.[21 64] Rodent models indicated an influence on the ATP levels, restoring cellular energy homeostasis[65] and an increased autophagy needed for the clearance of dysfunctional cell components.[64 66] Previous results, however, are not easily transferable to the general population, given that the included patients suffered from diabetes, which may interfere with AMD pathogenesis. A clinical trial investigating the safety and efficacy of metformin use to decrease GA progression in non-diabetic patients with dry AMD is being conducted at the moment (METforMIN, ClinicalTrials.gov: NCT02684578).[67]

We found no association of NSAIDs with prevalence of any or late AMD in our population. Similarly, previous literature on NSAIDs and AMD reported inconsistent results. A recent study on female teachers reported a reduced risk of AMD in a subset of low-dose acetylsalicylic acid (ASA) and cyclooxygenase-2 inhibitor users using longitudinal data[19] and another large-scale study found small effects of NSAID use on AMD incidence.[18] In contrast, results from an RCT did not show an effect of ASA use on progression to late AMD.[17] Particularly ASA, which is part of the group of NSAID and antithrombotic drugs, has been subject to various inhomogeneous studies and has even been reported to increase the risk of AMD.[68 69] Yet, OTC drugs are often used as needed and not regularly and as such may underlie a recall bias more than frequently used drugs. Hence, reliable assessments of OTC drugs are challenging and existing associations may be masked due to noise in the data.

We also found no association of L-dopa use and AMD in our data. Few previous studies reported L-dopa to affect a G protein-coupled receptor 143 on the RPE increasing its metabolism and suggested L-dopa as beneficial drug for treatment of AMD with less incident AMD and later onset as well as fewer needed intravitreal injections in exudative late AMD using longitudinal data.[22 70] This drug, however, is not frequently used in the general population and hence the absence of any association of L-dopa in our population is likely due to being statistically underpowered.

The strengths of this study include the large sample size combining data of 14 studies from central, Northern, Southern and Eastern Europe, which represents one of the largest studies on the association of systemic medications with AMD. AMD status was objectively assessed based on colour fundus photography in all studies using very similar and comparable classification systems. Image grading protocols differed slightly between studies but were either harmonised prior to our analysis or used comparable classification systems. Because a meta-analysis of all participating studies was conducted, results are not limited to one single study population only.

However, several limitations need to be considered. First, our study included cross-sectional data only. Thus, our findings display statistical association between drug use and AMD prevalence only and do not allow for the assessment of causality or risk. Assessments of systemic medication intake differed between studies and may be subject to re-call bias, misclassification or incomplete records. Moreover, duration of intake was not comprehensively assessed and we combined classes of drugs and did not differentiate between specific subtypes (eg, LLD included statins and fibrates, and antidiabetic drugs included oral drugs and insulin). Lastly, the prescription of any medication does not confirm the actual intake, which would be better represented by blood levels of the specific agent. These methodological differences may have introduced noise, reduced statistical precision and did not allow for assessments of drug–dose relationship. As expected, when combining different large-scale (population) studies, we observed between-study heterogeneity for different variables, which was addressed by using random-effect meta-analysis. Moreover, LIFE-Adult only provided data on early AMD, different to all other studies. Therefore, we performed a sensitivity analysis excluding LIFE-Adult, which did not change the results (data not shown). Moreover, variation in the classification of early and preclinical stages of AMD between studies may have created noise in the data and reduced statistical power. In contrast to small clinical studies, our large-scale population

studies did not have detailed information on disease severity, duration and variance of serum levels of glucose or lipids, which may provide more insight in underlying mechanisms.

The absence of detected associations with late AMD is likely due to a lack of statistical power caused by too few cases. Yet, AMD classification was based on fundus photography only. A multimodal approach including optical coherence tomography may have been more sensitive for subtle cases of late, particularly neovascular, AMD. Moreover, our population may underlie a potential survival bias of healthier participants or participants in which intake of drugs such as LLD and antidiabetic drugs do prolong the lifespan. Thus, late AMD cases may have died before enrolment in our studies. In contrast, some participants may also contribute to an indication bias; that is, individuals using these drugs are in worse general health and hence, given that AMD and CVD have been shown to be associated,[71] our detected associations may even be underestimated. A potential comorbidity of AMD with metabolic diseases such as diabetes and hyperlipidaemia may have contributed to the detected effects. The relation of diabetes and hyperlipidaemia with AMD is yet to be clarified and previous studies reported contradictive results.[72–74] In addition, there may have been a potential misclassification of AMD in few cases of severe diabetic retinopathy, which, again, could have introduced more noise into the data. We performed a sensitivity analysis stratifying AMD prevalence by disease status of diabetes and hyperlipidaemia (where data was available) and found no systematic bias in either direction (online supplemental table 1). Moreover, it is important to note that participants with diabetes and hyperlipidaemia were on average older and thus more likely to have AMD. Lastly, a potential synergistic effect of further drugs (eg, antihypertensive drugs) may have contributed to our results. We did adjust our models for prevalent hypertension, but residual confounding may be present. The combination of potential noise within medication and AMD data, the heterogeneity between studies and a possible selection bias of more healthy participants in large-scale (population) studies, may have reduced our statistical power and led to potentially underestimating detected associations. Lastly, all studies were mostly of Caucasian ethnicity and results may not be generalisable to other populations.[10]

In conclusion, our study suggests that regular intake of LLD and antidiabetic drugs is associated with reduced prevalence of AMD in the general population. Given a potential interference of these drugs with pathophysiological pathways relevant in AMD, this may contribute to a better understanding of AMD aetiology. Further longitudinal studies are needed to confirm or refute these associations.

Author affiliations
[1]Department of Ophthalmology, University Hospital Bonn, Bonn, Germany
[2]Department of Ophthalmology, Erasmus MC, Rotterdam, The Netherlands
[3]Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands
[4]Department of Ophthalmology, University Medical Center Mainz, Mainz, Germany
[5]NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust & UCL Institute of Ophthalmology, London, UK
[6]MRC Epidemiology Unit, University of Cambridge, Cambridge, UK
[7]Institute for Medical Informatics, Statistics and Epidemiology, Leipzig University, 04107 Leipzig, Germany
[8]Leipzig Research Centre for Civilization Diseases (LIFE), Leipzig University, 04103 Leipzig, Germany
[9]Leipzig University Medical Center, Medical Informatics Center - Dept. of Medical Data Science, 04107 Leipzig, Germany
[10]Department of Ophthalmology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[11]Institute of Molecular and Clinical Ophthalmology, Basel, Switzerland
[12]Ufa Eye Research Institute, Ufa, Russia
[13]Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland, UK
[14]Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, UMR 1219, Team LEHA, F-33000 Bordeaux, France
[15]Department of Community Medicine, UiT, The Arctic University of Norway, Tromsø, Norway
[16]Department of Ophthalmology, University Hospital of North Norway, Tromsø, Norway
[17]Directorate of eHealth, Oslo, Norway
[18]Department of Ophthalmology, Oslo University Hospital, Oslo, Norway
[19]Department of Ophthalmology, Aristotle University of Thessaloniki, School of Medicine, AHEPA Hospital, Thessaloniki, Greece
[20]Department of Genetic Epidemiology, University of Regensburg, Regensburg, Germany
[21]Department of Ophthalmology, University Hospital Regensburg, Regensburg, Germany
[22]Department of Ophthalmology, University Hospital Dijon, Dijon, France
[23]University of Münster, Faculty of Medicine, Institute of Epidemiology, Münster, Germany
[24]Department of Ophthalmology, St. Franzikus-Hospital, Münster, Germany
[25]AIBILI - Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal
[26]Univ Coimbra, Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, Coimbra, Portugal
[27]Univ Coimbra, Centre for Innovative Biomedicine and Biotechnology (CIBB), Coimbra, Portugal
[28]Padova-Camposampiero Hospital, Padova, Italy
[29]University of Padova, Department of Neuroscience, Padova, Italy
[30]Department of Ophthalmology, Gui de Chauliac Hospital, F-34000 Montpellier, France
[31]Institute for Neurosciences of Montpellier INM, Univ. Montpellier, INSERM, F-34091 Montpellier, France
[32]The Save Sight Institute, Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia

Twitter Ruth Hogg @ruth_hogg

Acknowledgements The authors are grateful to all participants as well as study assistants and technicians for their immense contribution within the respective studies.

Contributors MMM and RPF contributed to the conception and design, analysed data and wrote the initial version of the manuscript. TV, AKS, HE, NP, AK, RNL, PJF, FGR, KW, TK, JBJ, MMB, RH, TP, AC-G, GB, MGE, FT, DAG, CB, IMH, CPC-G, P-HG, H-WH, DP, PB, RC, SP, VD, FGH and CD performed data collection, contributed to study design and wrote the manuscript. All authors read and approved the final manuscript. Guarantor: MMM.

Funding 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. The Gutenberg Health Study is funded through the government of Rhineland-Palatinate ('Stiftung Rheinland-Pfalz fuer Innovation', contract AZ 961-386261/733), the research programmes 'Wissen schafft Zukunft' and 'Center for Translational Vascular Biology (CTVB)' of the Johannes Gutenberg University of Mainz, and its contract with Boehringer Ingelheim and PHILIPS Medical Systems, including an unrestricted grant for the Gutenberg Health Study. AKS holds the professorship for ophthalmic healthcare research endowed by 'Stiftung Auge' and financed by 'Deutsche Ophthalmologische Gesellschaft' and 'Berufsverband der Augenärzte Deutschland e.V.'. AugUR: Investigations and analyses are supported by grants from the German Federal Ministry of Education and Research (BMBF 01ER1206, BMBF 01ER1507 to IMH), by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation; HE 3690/7-1 and HE 3690/5-1 to IMH, BR 6028/2-1 to CB) and by the National Institutes of Health (NIH R01 EY RES 511967 to IMH). MARS (Münster Aging and Retina Study) was supported by Deutsche Forschungsgemeinschaft (DFG) Grants HE 2293/5-1, 5-2, 5-3 and PA 357/7-1, the Intramural International Monetary Fund of the University of Muenster, the Pro Retina Foundation and the Jackstaedt Foundation (DP, HWH). The EPIC-Norfolk study (DOI 10.22025/2019.10.105.00004) has received funding from the Medical Research Council (MR/N003284/1 and MC-UU_12015/1) and Cancer Research UK (C864/A14136). The clinic for the third health examination was funded by Research into Ageing (262). We are grateful to all the participants who have been part of the project and to the many members of the study teams at the University of Cambridge who have enabled this research. AK is funded by a UKRI Future Leaders Fellowship (Medical Research Council MR/T040912/1). RNL is funded by a Moorfields Eye Charity Springboard Award. PJF is supported by an unrestricted grant from Alcon and the Desmond Foundation. This publication is supported by the Leipzig Research Centre for Civilization Diseases (LIFE), an organisational unit affiliated to the Medical Faculty of Leipzig University. LIFE is funded by means of the European Union, by the European Regional Development Fund (ERDF) and by funds of the Free State

of Saxony within the framework of the excellence initiative (project numbers: 713-241202, 14505/2470, 14575/2470). FGR is supported by a grant from the German Federal Ministry of Education and Research: i:DSem—Integrative data semantics in systems medicine (031L0026). The authors wish to express their sincere thanks to the participants of LIFE-Adult for their time. The authors gratefully acknowledge KW and her team at the Leipzig Research Center for Civilization Diseases (LIFE-Adult), Leipzig University, Leipzig, Germany for data acquisition. The NICOLA study is funded by the Atlantic Philanthropies, the Economic and Social Research Council, the UKCRC Centre of Excellence for Public Health Northern Ireland, the Centre for Aging Research and Development in Ireland, the Office of the First Minister and Deputy First Minister, the Health and Social Care Research and Development Division of the Public Health Agency, the Wellcome Trust/Wolfson Foundation and Queen's University Belfast. CRESCENDO study was carried out with the financial support of the ANR—Agence Nationale de la Recherche (MALZ-007-01—The French National Research Agency—and grants from the "Chercheur d'Avenir" (R12028FF) and Aide à la Recherche en Partenariat avec les Entreprises (ARPE; RPH12007F) allocated by the Languedoc Roussillon administrative regional district (France). The Coimbra Eye Study was funded by Novartis.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. This current study is based on previously assessed granular data from 14 studies. Therefore, no ethical approval for this current study is necessary. All 14 included studies adhered to the tenets of the Declaration of Helsinki and had local ethical committee approval (see key references of individual studies). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. Study data may be available upon reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Matthias M Mauschitz http://orcid.org/0000-0002-5605-8207
Paul J Foster http://orcid.org/0000-0002-4755-177X
Jost B Jonas http://orcid.org/0000-0003-2972-5227
Ruth Hogg http://orcid.org/0000-0001-9413-2669
Tunde Peto http://orcid.org/0000-0001-6265-0381
Maja Gran Erke http://orcid.org/0000-0002-7476-0286
Dimitrios A Giannoulis http://orcid.org/0000-0002-7795-2152
Pierre-Henry Gabrielle http://orcid.org/0000-0002-9688-4845
Vincent Daien http://orcid.org/0000-0001-5675-0861
Cecile Delcourt http://orcid.org/0000-0002-2099-0481

REFERENCES

1 Wong WL, Su X, Li X, *et al*. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health* 2014;2:e106–16.
2 Finger RP, Fimmers R, Holz FG, *et al*. Prevalence and causes of registered blindness in the largest federal state of Germany. *Br J Ophthalmol* 2011;95:1061–7.
3 Li JQ, Welchowski T, Schmid M, *et al*. Prevalence and incidence of age-related macular degeneration in Europe: a systematic review and meta-analysis. *Br J Ophthalmol* 2020;104:1077–84.
4 Spaide RF, Jaffe GJ, Sarraf D, *et al*. Consensus Nomenclature for reporting neovascular age-related macular degeneration data: consensus on neovascular age-related macular degeneration nomenclature Study Group. *Ophthalmology* 2020;127:616–36.
5 Choudhary M, Malek G. A Review of Pathogenic Drivers of Age-Related Macular Degeneration, Beyond Complement, with a Focus on Potential Endpoints for Testing Therapeutic Interventions in Preclinical Studies. *Adv Exp Med Biol* 2019;1185:9–13.
6 Heesterbeek TJ, Lorés-Motta L, Hoyng CB, *et al*. Risk factors for progression of age-related macular degeneration. *Ophthalmic Physiol Opt* 2020;40:140–70.
7 Colijn JM, Buitendijk GHS, Prokofyeva E, *et al*. Prevalence of age-related macular degeneration in Europe: the past and the future. *Ophthalmology* 2017;124:1753–63.
8 McGuinness MB, Le J, Mitchell P, *et al*. Physical activity and age-related macular degeneration: a systematic literature review and meta-analysis. *Am J Ophthalmol* 2017;180:29–38.
9 Jarrett SG, Boulton ME. Consequences of oxidative stress in age-related macular degeneration. *Mol Aspects Med* 2012;33:399–417.
10 Mauschitz MM, Schmitz M-T, Verzijden T, *et al*. Physical activity, incidence, and progression of age-related macular degeneration: a Multicohort study. *Am J Ophthalmol* 2022;236:99–106.
11 Kersten E, Dammeier S, Ajana S, *et al*. Metabolomics in serum of patients with non-advanced age-related macular degeneration reveals aberrations in the glutamine pathway. *PLoS One* 2019;14:e0218457.
12 Colijn JM, den Hollander AI, Demirkan A, *et al*. Increased high-density lipoprotein levels associated with age-related macular degeneration: evidence from the EYE-RISK and European eye epidemiology consortia. *Ophthalmology* 2019;126:393–406.
13 Jun S, Datta S, Wang L, *et al*. The impact of lipids, lipid oxidation, and inflammation on AMD, and the potential role of miRNAs on lipid metabolism in the RPE. *Exp Eye Res* 2019;181:346–55.
14 Curcio CA, Presley JB, Malek G, *et al*. Esterified and unesterified cholesterol in drusen and basal deposits of eyes with age-related maculopathy. *Exp Eye Res* 2005;81:731–41.
15 Colijn JM, Meester-Smoor M, Verzijden T, *et al*. Genetic risk, lifestyle, and age-related macular degeneration in Europe: the EYE-RISK Consortium. *Ophthalmology* 2021;128:1039–49.
16 Roizenblatt M, Naranjit N, Maia M, *et al*. The question of a role for statins in age-related macular degeneration. *Int J Mol Sci* 2018;19:3688.
17 Keenan TD, Wiley HE, Agrón E, *et al*. The association of aspirin use with age-related macular degeneration progression in the age-related eye disease studies: age-related eye disease study 2 report No. 20. *Ophthalmology* 2019;126:1647–56.
18 Modjtahedi BS, Fong DS, Jorgenson E, *et al*. The relationship between nonsteroidal anti-inflammatory drug use and age-related macular degeneration. *Am J Ophthalmol* 2018;188:111–22.
19 Xu X, Ritz B, Coleman AL, *et al*. Non-Steroidal anti-inflammatory drug use and risk of age-related macular degeneration in the California teachers study. *Drugs Aging* 2021;38:817–28.
20 Stewart JM, Lamy R, Wu F, *et al*. Relationship between oral metformin use and age-related macular degeneration. *Ophthalmol Retina* 2020;4:1118–9.
21 Blitzer AL, Ham SA, Colby KA, *et al*. Association of metformin use with age-related macular degeneration: a case-control study. *JAMA Ophthalmol* 2021;139:302–9.
22 Figueroa AG, Boyd BM, Christensen CA, *et al*. Levodopa positively affects neovascular age-related macular degeneration. *Am J Med* 2021;134:122–8.
23 Fuentes A, Pineda M, Venkata K. Comprehension of top 200 prescribed drugs in the US as a resource for pharmacy teaching, training and practice. *Pharmacy* 2018;6:43.
24 Schwabe U, Ludwig W-D. *Arzneiverordnungs-Report 2020*. Springer, 2020.
25 Wehling M. Non-steroidal anti-inflammatory drug use in chronic pain conditions with special emphasis on the elderly and patients with relevant comorbidities: management and mitigation of risks and adverse effects. *Eur J Clin Pharmacol* 2014;70:1159–72.
26 Ma L, Wang Y, Du J, *et al*. The association between statin use and risk of age-related macular degeneration. *Sci Rep* 2015;5:18280.
27 Klein R, Klein BEK, Tomany SC, *et al*. Relation of statin use to the 5-year incidence and progression of age-related maculopathy. *Arch Ophthalmol* 2003;121:1151–5.
28 VanderBeek BL, Zacks DN, Talwar N, *et al*. Role of statins in the development and progression of age-related macular degeneration. *Retina* 2013;33:414–22.
29 Guymer RH, Baird PN, Varsamidis M, *et al*. Proof of concept, randomized, placebo-controlled study of the effect of simvastatin on the course of age-related macular degeneration. *PLoS One* 2013;8:e83759.
30 Cackett P, Wong TY, Aung T, *et al*. Smoking, cardiovascular risk factors, and age-related macular degeneration in Asians: the Singapore Malay eye study. *Am J Ophthalmol* 2008;146:960–7.
31 Fong DS, Contreras R. Recent statin use and 1-year incidence of exudative age-related macular degeneration. *Am J Ophthalmol* 2010;149:955–8.
32 Barbosa DTQ, Mendes TS, Cíntron-Colon HR, *et al*. Age-Related macular degeneration and protective effect of HMG Co-a reductase inhibitors (statins): results from the National health and nutrition examination survey 2005-2008. *Eye* 2014;28:472–80.
33 Delcourt C, Korobelnik J-F, Buitendijk GHS, *et al*. Ophthalmic epidemiology in Europe: the "European Eye Epidemiology" (E3) consortium. *Eur J Epidemiol* 2016;31:197–210.
34 Brandl C, Zimmermann ME, Günther F, *et al*. On the impact of different approaches to classify age-related macular degeneration: results from the German augur study. *Sci Rep* 2018;8:8675.
35 Farinha CVL, Cachulo ML, Alves D, *et al*. Incidence of Age-Related Macular Degeneration in the Central Region of Portugal: The Coimbra Eye Study - Report 5. *Ophthalmic Res* 2019;61:226–35.
36 Yip JLY, Khawaja AP, Chan MPY, *et al*. Area deprivation and age related macular degeneration in the EPIC-Norfolk eye study. *Public Health* 2015;129:103–9.
37 Höhn R, Kottler U, Peto T, *et al*. The ophthalmic branch of the Gutenberg health study: study design, cohort profile and self-reported diseases. *PLoS One* 2015;10:e0120476.
38 Loeffler M, Engel C, Ahnert P, *et al*. The LIFE-Adult-Study: objectives and design of a population-based cohort study with 10,000 deeply phenotyped adults in Germany. *BMC Public Health* 2015;15:691.

39 McCann P, Hogg R, Wright DM, *et al*. Glaucoma in the Northern Ireland cohort for the longitudinal study of ageing (NICOLA): cohort profile, prevalence, awareness and associations. *Br J Ophthalmol* 2020;104:1492–9.
40 Bikbov M, Fayzrakhmanov RR, Kazakbaeva G, *et al*. Ural eye and medical study: description of study design and methodology. *Ophthalmic Epidemiol* 2018;25:187–98.
41 Wang JJ, Rochtchina E, Lee AJ, *et al*. Ten-Year incidence and progression of age-related maculopathy: the blue Mountains eye study. *Ophthalmology* 2007;114:92–8.
42 Thee EF, Meester-Smoor MA, Luttikhuizen DT, *et al*. Performance of classification systems for age-related macular degeneration in the Rotterdam study. *Transl Vis Sci Technol* 2020;9:26.
43 Korb CA, Elbaz H, Schuster AK, *et al*. Five-Year cumulative incidence and progression of age-related macular degeneration: results from the German population-based Gutenberg health study (GHS). *Graefes Arch Clin Exp Ophthalmol* 2022;260:55–64.
44 Ferris FL, Wilkinson CP, Bird A, *et al*. Clinical classification of age-related macular degeneration. *Ophthalmology* 2013;120:844–51.
45 Mauschitz MM, Bonnemaijer PWM, Diers K, *et al*. Systemic and ocular determinants of peripapillary retinal nerve fiber layer thickness measurements in the European eye epidemiology (E3) population. *Ophthalmology* 2018;125:1526–36.
46 Gehlbach P, Li T, Hatef E. Statins for age-related macular degeneration. *Cochrane Database Syst Rev* 2016:CD006927.
47 Vavvas DG, Daniels AB, Kapsala ZG, *et al*. Regression of some high-risk features of age-related macular degeneration (AMD) in patients receiving intensive statin treatment. *EBioMedicine* 2016;5:198–203.
48 Al-Holou SN, Tucker WR, Agrón E, *et al*. The association of statin use with age-related macular degeneration progression: the age-related eye disease study 2 report number 9. *Ophthalmology* 2015;122:2490–6.
49 Maguire MG, Ying G-shuang, McCannel CA, *et al*. Statin use and the incidence of advanced age-related macular degeneration in the complications of age-related macular degeneration prevention trial. *Ophthalmology* 2009;116:2381–5.
50 Shalev V, Sror M, Goldshtein I, *et al*. Statin use and the risk of age related macular degeneration in a large health organization in Israel. *Ophthalmic Epidemiol* 2011;18:83–90.
51 Lee H, Jeon HL, Park SJ, *et al*. Effect of statins, metformin, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers on age-related macular degeneration. *Yonsei Med J* 2019;60:679–86.
52 Ludwig CA, Vail D, Rajeshuni NA, *et al*. Statins and the progression of age-related macular degeneration in the United States. *PLoS One* 2021;16:e0252878.
53 Lin JB, Halawa OA, Husain D, *et al*. Dyslipidemia in age-related macular degeneration. *Eye* 2022;36:312–8.
54 Eshtiaghi A, Popovic MM, Sothivannan A, *et al*. Statin use and the incidence of age-related macular degeneration: a meta-analysis. *Retina* 2022;42:643–52.
55 Memarzadeh E, Heidari-Soureshjani S. The relationship between statin and risk of age-related macular degeneration: a systematic review and meta-analysis. *J Ophthalmol* 2022;2022:1–9.
56 Fan Q, Maranville JC, Fritsche L, *et al*. HDL-cholesterol levels and risk of age-related macular degeneration: a multiethnic genetic study using Mendelian randomization. *Int J Epidemiol* 2017;46:1891–902.
57 Betzler BK, Rim TH, Sabanayagam C, *et al*. High-Density lipoprotein cholesterol in age-related ocular diseases. *Biomolecules* 2020;10:645.
58 McTaggart F, Jones P. Effects of statins on high-density lipoproteins: a potential contribution to cardiovascular benefit. *Cardiovasc Drugs Ther* 2008;22:321–38.
59 Barter PJ, Brandrup-Wognsen G, Palmer MK, *et al*. Effect of statins on HDL-C: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER database. *J Lipid Res* 2010;51:1546–53.
60 Ooi KG-J, Khoo P, Vaclavik V, *et al*. Statins in ophthalmology. *Surv Ophthalmol* 2019;64:401–32.
61 Chen Y-Y, Shen Y-C, Lai Y-J, *et al*. Association between metformin and a lower risk of age-related macular degeneration in patients with type 2 diabetes. *J Ophthalmol* 2019;2019:1–9.
62 Brown EE, Ball JD, Chen Z, *et al*. The common antidiabetic drug metformin reduces odds of developing age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2019;60:1470–7.
63 Eton EA, Wubben TJ, Besirli CG, *et al*. Association of metformin and development of dry age-related macular degeneration in a U.S. insurance claims database. *Eur J Ophthalmol* 2022;32:417–23.
64 Romdhoniyyah DF, Harding SP, Cheyne CP, *et al*. Metformin, a potential role in age-related macular degeneration: a systematic review and meta-analysis. *Ophthalmol Ther* 2021;10:245–60.
65 Rabinovitch RC, Samborska B, Faubert B, *et al*. Ampk maintains cellular metabolic homeostasis through regulation of mitochondrial reactive oxygen species. *Cell Rep* 2017;21:1–9.
66 Chun Y, Kim J. Autophagy: an essential degradation program for cellular homeostasis and life. *Cells* 2018;7:278.
67 Asahi MG, Avaylon J, Wallsh J, *et al*. Emerging biological therapies for the treatment of age-related macular degeneration. *Expert Opin Emerg Drugs* 2021;26:193–207.
68 Ye J, Xu Y-F, He J-J, *et al*. Association between aspirin use and age-related macular degeneration: a meta-analysis. *Invest Ophthalmol Vis Sci* 2014;55:2687–96.
69 Lee W-JA, Yang Y-HK, Cheng C-L. Risk of age-related macular degeneration in aspirin users and non-aspirin users: a population-based cohort study in Taiwan. *Pharmacoepidemiol Drug Saf* 2021;30:178–88.
70 Brilliant MH, Vaziri K, Connor TB, *et al*. Mining retrospective data for virtual prospective drug repurposing: L-dopa and age-related macular degeneration. *Am J Med* 2016;129:292–8.
71 Mauschitz MM, Finger RP. Age-Related macular degeneration and cardiovascular diseases: revisiting the common soil theory. *Asia Pac J Ophthalmol* 2022;11:94–9.
72 Zhang YP, Wang YX, Zhou JQ, *et al*. The influence of diabetes, hypertension, and hyperlipidemia on the onset of age-related macular degeneration in North China: the Kailuan eye study. *Biomed Environ Sci* 2022;35:613–21.
73 Vassilev ZP, Ruigómez A, Soriano-Gabarró M, *et al*. Diabetes, cardiovascular morbidity, and risk of age-related macular degeneration in a primary care population. *Invest Ophthalmol Vis Sci* 2015;56:1585–92.
74 He M-S, Chang F-L, Lin H-Z, *et al*. The association between diabetes and age-related macular degeneration among the elderly in Taiwan. *Diabetes Care* 2018;41:2202–11.

Discussion

The thesis herein comprises four studies using different epidemiological approaches and statistical methods to analyze specific ophthalmic datasets and to address respective research questions. The examples of different available data from diverse cohorts underline the importance of epidemiologic research which goes beyond simply applying statistics. The four studies investigate various topics (rare outcome in **Study 1**, biomarker generation within the general population in **Study 2**, and identification of determinants of frequent diseases in **Studies 3 and 4**) and therefore needed different epidemiological approaches. Apart from answers to the underlying research questions, the composition of this thesis illustrates the diversity of epidemiological research methods and underscores the significance of inspecting the available data in order to choose the appropriate settings and statistics and to avoid misinterpretation, e.g. by confounding or bias.

By harmonizing and pooling data from relatively similar source cohorts (German and Swiss patients) in **Study 1** we were able to receive a “real world dataset” of 133 patients with pre- and postoperative assessments, which allowed for robust statistical analyses. Our study confirmed the positive effect of the Yokoyama procedure on strabismus due to high myopia. However, residual heterogeneity between different sites may have hampered statistical power and needs to be acknowledged as potential limitation. We could not find an additional effect of MMR on the postoperative outcomes, which seemed to be mainly driven by the amount of preoperative esotropia. Yet, additional MMR may be helpful in cases of muscle contracture hampering union of the superior and later rectus muscle.

In the **second Study** of this thesis we investigated the associations of various SD-OCT-based retinal layer assessments and MRI – based brain measurements in order to evaluate their potential usability as biomarker of brain atrophy in 2872 participants of the Rhineland Study. To date, our study provides one of the largest datasets using high-resolution SD-OCT of the retina and 3 Tesla (T) – MRI imaging of the brain. We found assessments of the inner retina both, at the macula and the optic disc, to be mainly associated with WM volume, which

was even stronger within the occipital lobe and the hippocampus. In addition, diffusion tensor imaging (DTI) assessments as proxy of WM integrity showed similar association with the inner retina.

Most of the few previous studies on the relation of retinal layers and brain measurements were based on small cohorts of healthy and neurologically impaired participants, focused on the inner retina only, and reported partially conflicting results. (Ong et al., 2015; Casaletto et al., 2017; Sung et al., 2019) The Rotterdam Study is the only population-based study with large data on the relation between retinal imaging and brain assessments and reported strong associations of the innermost retinal layers with both, GM and WM volumes and partly with FA in DTI imaging. Yet, the authors were only able to assess the innermost retinal layers due to older OCT-devices and less precise segmentation algorithms. (Mutlu et al., 2017; Mutlu et al., 2018b)

Our studies confirms these results and moreover extends them in that we found associations with various brain structures and with an additional inner retinal layer at the macula (macular inner nuclear layer, mINL). Moreover, we were able to delineate the outer retina and found an association of the RPE with total brain volume (TBV), which was mainly driven by GM volume. So far, only two small studies with 52 and 64 subjects, respectively, investigated the relation of the outer retina and MRI-based brain assessments using very simple statistical methods only and reported inconsistent results. (Jorge et al., 2019; Uchida et al., 2020) The underlying pathomechanisms of the associations of different parts of the retina and the brain remain to be elucidated. The association with the inner retina was previously hypothesized as direct retrograde degeneration, leading from cortical atrophy via reduced neuronal inter-connections to decline of retinal axons. (Mutlu et al., 2018b; Mutlu et al., 2018a) This close anatomical connection, however, does not apply to the outer retina, where systemic changes e.g. associated with impaired perfusion or other vascular pathology may play a role. The mRPE contains highly metabolically active cells supporting photoreceptors in the maintenance of the visual cycle, contributes to the blood-retina barrier, and is not part of the neuro-sensory retina with direct connection to cerebral neurons. (Vinores, 1995) This may

explain why we found no association of mRPE with WM volumes as we did for the inner retina. Hence, we speculate that mechanisms for mRPE are less direct and represent a more general metabolic dysregulation. Interestingly, we found the overall strongest associations with volumes of the hippocampi. As the hippocampi decline early in the course of cognitive impairment (Tabatabaei-Jafari et al., 2015), retinal layers may have value as accessible biomarker of hippocampus atrophy and cognitive decline. Common limitations to population studies are a potential self-selection bias as well as a recall-bias in self-reported diseases and may as well have affected our study. Yet, we consider it most likely that it may have led to an underestimation of effects due to more noise in the data and thus less statistical power. Our data suggest that SD-OCT assessments of retinal layers may be useful as additional examination in the longitudinal monitoring of specific neurological and neurodegenerative diseases including brain atrophy.

In the **third Study** we investigated the impact of PA on the incidence and progression of AMD. Our study indicates a protective effect of high levels of PA against the development of early AMD using longitudinal data of 14,630 subjects. As mentioned above, previous studies were based on small sample size, cross-sectional data and/or reported conflicting results. (Knudtson et al., 2006; Gopinath et al., 2014) Our results are in agreement with the previously reported association of low PA with higher AMD prevalence based on cross-sectional data and stress the role of PA as a modifiable lifestyle risk factor. The underlying mechanisms, however, remain unclear. Regular PA has been shown to increase antioxidant activity and reduce chronic inflammation as well as oxidative stress. The latter has been associated with cellular damage, diminished vascular endothelial function, and increased inflammation and has also been identified as pathogenetic component in AMD. (Reuter et al., 2010; Mury et al., 2018; Heesterbeek et al., 2020) Hence, reduced oxidative stress may contribute to the protective effect of PA on AMD development. The main limitation of this study is the self-reported PA, which may have introduced noise in the data and did not allow for a dose-response relationship. Again, this may have likely caused an underestimation of

effects and unlikely caused false positive findings. Based on our results, recommendations for prevention within the public health sector ought to include regular PA.

In the **fourth Study** we evaluated associations of frequently used systemic medications, in particular lipid-lowering drugs, anti-diabetic drugs, non-steroidal anti-inflammatory drugs (NSAID), and Levodopa (L-Dopa), with AMD prevalence in 38,694 subjects. We found that use of lipid-lowering and anti-diabetic drugs was associated with lower prevalence of total AMD. We found no relation with late AMD or with use of NSAID and L-Dopa, which may be due to a lack of statistical power, potential survival bias and/or no existing effect. Our study indicates a potential beneficial effect of these drugs on AMD prevalence and support the relevance of metabolic processes in its multifactorial pathogenesis.

Earlier studies on these associations included varying sample size and reported partly inconsistent results. (Klein et al., 2003; Guymer et al., 2013; VanderBeek et al., 2013; Le Ma et al., 2015; Lee et al., 2019; Stewart et al., 2020) Our study suggests a beneficial association of LLD and anti-diabetic drugs with AMD and represents the first study meta-analyzing granular data from various large-scale studies. LLD and anti-diabetic drugs (mainly metformin) have previously been reported to have anti-inflammatory and anti-oxidant actions, which may explain their potentially beneficial role. (Jarrett and Boulton, 2012; Roizenblatt et al., 2018; Heesterbeek et al., 2020; Blitzer et al., 2021; Romdhoniyyah et al., 2021) In addition, LLD are known to lower serum levels of low-density lipoprotein (LDL). Interestingly, several studies reported an increased risk of AMD with higher levels of HDL, which, in contrast to LDL, is generally assumed beneficial in CVD. (Fan et al., 2017; Colijn et al., 2019) Given that statins have been reported to increase serum levels of HDL-C, these studies are partly inconsistent with our results and underline the need for further large-scale longitudinal studies. (McTaggart and Jones, 2008; Barter et al., 2010) The main limitation of this study is the cross-sectional nature, which did not allow for assessment of causality or risk and showed statistical associations, only. Given a potential interference of LLD and anti-diabetic drugs with pathophysiological pathways relevant in AMD, our data can contribute to a better understanding of AMD etiology.

Summary and outlook

In this thesis different epidemiological approaches were used to gather and evaluate various large datasets in order to address specific research questions in the field of ophthalmology. According to the individual research questions and the scientific intention it is crucial to select the adequate and preferred data and corresponding analysis plan à priori.

Within the different projects we underscore the entanglement of the eyes with the rest of the body. Our data indicate a close relation of AMD with several factors that play a role in other age-related systemic diseases. We provide evidence for a beneficial impact of high physical activity (PA) on AMD development. In absence of physical disabilities, PA can relatively simply be increased and therefore contribute to a lower risk not only for AMD but also for cardiovascular disease and general health. (Warburton and Bredin, 2017; Jeong et al., 2019) The World Health Organization (WHO) recommends 150-300 minutes of moderate-intensity aerobic PA, which corresponds to only ca. 20 minutes per day. (World Health Organization, 2020) Moreover, previous studies reported the beneficial effect of PA to occur even below WHO recommendations and irrespective of past PA levels. (Wen et al., 2011; Mok et al., 2019) Future public health messages on AMD prevention strategies should include high PA as modifiable risk factor. In addition, we found a lower prevalence of any AMD in participants who used lipid-lowering and anti-diabetic drugs. Firstly, our data indicate the involvement of both, the lipid metabolism and oxidative stress in AMD pathogenesis. This merits further studies on specifically involved metabolites and processes, e.g. using metabolomics analysis approaches. Secondly, particularly given the highly frequent use of these drugs, additional longitudinal studies are needed to re-evaluate our findings and establish therapy recommendations. Previous RCT data failed to show an explicit effect of statins on AMD development (Maguire et al., 2009; Guymer et al., 2013) Hence, further RCT may need to stratify into different subgroups (healthy individuals, patients at high risk for AMD, patients with hypercholesterolemia etc.) to account for the complexity of AMD.

Apart from AMD, we identified several potential ophthalmic biomarkers for systemic neurodegenerative diseases resulting in brain atrophy using large-scale population data. We provide state-of-the-art high-resolution imaging data which is not restricted to the inner layers of the retina only. Implications include the usefulness of retinal measurements in the longitudinal monitoring of neurological and neurodegenerative diseases that can cause brain atrophy. Clinical studies with respective patients are needed to evaluate the associations and feasibility over time and in case of disease progression.

Lastly, we used multicenter data and epidemiological analyses to confirm the usability of the Yokoyama procedure in esotropic patients with high myopia. We found the pre-operative angle to be the largest determinant of post-operative angle and did not find any effect of an additional recession of the medial rectus muscle. Even though or dataset represents one of the largest “real world datasets” on this procedure we may still have missed any subtle impact due to insufficient statistical power or any potential residual selection bias within the cohorts. Future studies with longer follow-up data ought to evaluate the long-term effects after Yokoyama procedure.

The composition of this thesis underscores the relevance of international collaborations in ophthalmic research. Through the European cooperation within E3, scientists from Northern, Eastern, Southern and Central Europe from more than 30 institutions work together and are in constant exchange. This collaboration enables gathering these large and more informative datasets and investigating relations more precisely. To our knowledge, there is no comparable collaboration of international studies with such a large data pool, making E3 a unique platform for ophthalmo-epidemiologic research.

In conclusion, the thesis highlights the advantages and benefits of analyzing large-scale high-quality datasets and illustrates the need for various analytical approaches. By doing so we were able to provide answers to specific relevant research questions that have not been sufficiently addressed before. Previous evidence on the relation of AMD with PA and systemic medication was either incoherent or insufficient and based on smaller cohorts. Thus

far, evaluations of the usefulness of SD-OCT-based retinal measurements as biomarkers for brain atrophy was hampered by technical limitations or small sample size and the few existing studies on the effects of the Yokoyama procedure were limited by small case numbers of non-European patients. Hence, the included studies of this thesis enhanced the knowledge within the field of ophthalmo-epidemiology and lay foundation for further (international) collaborations.

Overlap due to shared authorships

No overlap with other habilitation theses needs to be declared. None of the four papers of this thesis involve shared authorships. This thesis contains one last authorship (**Study 1**) and three first authorships (**Studies 2 – 4**) of the habilitation candidate.

Bibliography

References

Barter, P.J., Brandrup-Wognsen, G., Palmer, M.K., and Nicholls, S.J. (2010). Effect of statins on HDL-C: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER Database. Journal of lipid research *51*, 1546-1553. https://doi.org/10.1194/jlr.P002816.

Bhopal, R., Macfarlane, G.J., Smith, W.C., and West, R. (2011). What is the future of epidemiology? Lancet (London, England) *378*, 464-465. https://doi.org/10.1016/S0140-6736(11)61147-1.

Blitzer, A.L., Ham, S.A., Colby, K.A., and Skondra, D. (2021). Association of Metformin Use With Age-Related Macular Degeneration: A Case-Control Study. JAMA ophthalmology *139*, 302-309. https://doi.org/10.1001/jamaophthalmol.2020.6331.

Britze, J., and Frederiksen, J.L. (2018). Optical coherence tomography in multiple sclerosis. Eye (London, England) *32*, 884-888. https://doi.org/10.1038/s41433-017-0010-2.

Brown, G.C., Brown, M.M., Sharma, S., Stein, J.D., Roth, Z., Campanella, J., and Beauchamp, G.R. (2005). The burden of age-related macular degeneration: a value-based medicine analysis. Transactions of the American Ophthalmological Society *103*, 173-84; discussion 184-6.

Casaletto, K.B., Ward, M.E., Baker, N.S., Bettcher, B.M., Gelfand, J.M., Li, Y., Chen, R., Dutt, S., Miller, B., and Kramer, J.H., et al. (2017). Retinal thinning is uniquely associated with medial temporal lobe atrophy in neurologically normal older adults. Neurobiology of aging *51*, 141-147. https://doi.org/10.1016/j.neurobiolaging.2016.12.011.

Chang, L.Y.L., Lowe, J., Ardiles, A., Lim, J., Grey, A.C., Robertson, K., Danesh-Meyer, H., Palacios, A.G., and Acosta, M.L. (2014). Alzheimer's disease in the human eye. Clinical tests that identify ocular and visual information processing deficit as biomarkers. Alzheimer's & dementia : the journal of the Alzheimer's Association *10*, 251-261. https://doi.org/10.1016/j.jalz.2013.06.004.

Choudhary, M., and Malek, G. (2019). A Review of Pathogenic Drivers of Age-Related Macular Degeneration, Beyond Complement, with a Focus on Potential Endpoints for Testing Therapeutic Interventions in Preclinical Studies. Advances in experimental medicine and biology *1185*, 9-13. https://doi.org/10.1007/978-3-030-27378-1_2.

Colijn, J.M., Buitendijk, G.H.S., Prokofyeva, E., Alves, D., Cachulo, M.L., Khawaja, A.P., Cougnard-Gregoire, A., Merle, B.M.J., Korb, C., and Erke, M.G., et al. (2017). Prevalence of Age-Related Macular Degeneration in Europe: The Past and the Future. Ophthalmology *124*, 1753-1763. https://doi.org/10.1016/j.ophtha.2017.05.035.

Colijn, J.M., Hollander, A.I. den, Demirkan, A., Cougnard-Grégoire, A., Verzijden, T., Kersten, E., Meester-Smoor, M.A., Merle, B.M.J., Papageorgiou, G., and Ahmad, S., et al. (2019). Increased High-Density Lipoprotein Levels Associated with Age-Related Macular Degeneration: Evidence from the EYE-RISK and European Eye Epidemiology Consortia. Ophthalmology *126*, 393-406. https://doi.org/10.1016/j.ophtha.2018.09.045.

Colijn, J.M., Meester-Smoor, M., Verzijden, T., Breuk, A. de, Silva, R., Merle, B.M.J., Cougnard-Grégoire, A., Hoyng, C.B., Fauser, S., and Coolen, A., et al. (2021). Genetic Risk, Lifestyle, and Age-Related Macular Degeneration in Europe: The EYE-RISK Consortium. Ophthalmology *128*, 1039-1049. https://doi.org/10.1016/j.ophtha.2020.11.024.

Curcio, C.A., Presley, J.B., Malek, G., Medeiros, N.E., Avery, D.V., and Kruth, H.S. (2005). Esterified and unesterified cholesterol in drusen and basal deposits of eyes with age-related maculopathy. Experimental eye research *81*, 731-741. https://doi.org/10.1016/j.exer.2005.04.012.

DAWBER, T.R., MEADORS, G.F., and MOORE, F.E. (1951). Epidemiological approaches to heart disease: the Framingham Study. American journal of public health and the nation's health *41*, 279-281. https://doi.org/10.2105/ajph.41.3.279.

Delcourt, C., Korobelnik, J.-F., Buitendijk, G.H.S., Foster, P.J., Hammond, C.J., Piermarocchi, S., Peto, T., Jansonius, N., Mirshahi, A., and Hogg, R.E., et al. (2016). Ophthalmic epidemiology in Europe: the "European Eye Epidemiology" (E3) consortium. European journal of epidemiology *31*, 197-210. https://doi.org/10.1007/s10654-015-0098-2.

(2018). Epidemiology is a science of high importance. Nature communications *9*, 1703. https://doi.org/10.1038/s41467-018-04243-3.

Ertl, B., Hartmann, F.G., and Heine, J.-H. (2020). Analyzing Large-Scale Studies: Benefits and Challenges. Frontiers in psychology *11*, 577410. https://doi.org/10.3389/fpsyg.2020.577410.

Fan, Q., Maranville, J.C., Fritsche, L., Sim, X., Cheung, C.M.G., Chen, L.J., Gorski, M., Yamashiro, K., Ahn, J., and Laude, A., et al. (2017). HDL-cholesterol levels and risk of age-related macular degeneration: a multiethnic genetic study using Mendelian randomization. International journal of epidemiology *46*, 1891-1902. https://doi.org/10.1093/ije/dyx189.

Ferris, F.L., Wilkinson, C.P., Bird, A., Chakravarthy, U., Chew, E., Csaky, K., and Sadda, S.R. (2013). Clinical classification of age-related macular degeneration. Ophthalmology *120*, 844-851. https://doi.org/10.1016/j.ophtha.2012.10.036.

Finger, R.P. (2007). Blindheit in Deutschland: Dimensionen und Perspektiven. Der Ophthalmologe : Zeitschrift der Deutschen Ophthalmologischen Gesellschaft *104*, 839-844. https://doi.org/10.1007/s00347-007-1600-3.

Finger, R.P., Fimmers, R., Holz, F.G., and Scholl, H.P.N. (2011). Prevalence and causes of registered blindness in the largest federal state of Germany. The British journal of ophthalmology *95*, 1061-1067. https://doi.org/10.1136/bjo.2010.194712.

Francula-Zaninovic, S., and Nola, I.A. (2018). Management of Measurable Variable Cardiovascular Disease' Risk Factors. Current cardiology reviews *14*, 153-163. https://doi.org/10.2174/1573403X14666180222102312.

Frérot, M., Lefebvre, A., Aho, S., Callier, P., Astruc, K., and Aho Glélé, L.S. (2018). What is epidemiology? Changing definitions of epidemiology 1978-2017. PloS one *13*, e0208442. https://doi.org/10.1371/journal.pone.0208442.

Fuentes, A.V., Pineda, M.D., and Venkata, K.C.N. (2018). Comprehension of Top 200 Prescribed Drugs in the US as a Resource for Pharmacy Teaching, Training and Practice. Pharmacy (Basel, Switzerland) *6*. https://doi.org/10.3390/pharmacy6020043.

Gopinath, B., Liew, G., Burlutsky, G., and Mitchell, P. (2014). Physical activity and the 15-year incidence of age-related macular degeneration. Investigative ophthalmology & visual science *55*, 7799-7803. https://doi.org/10.1167/iovs.14-15575.

Grande, G., Qiu, C., and Fratiglioni, L. (2020). Prevention of dementia in an ageing world: Evidence and biological rationale. Ageing research reviews *64*, 101045. https://doi.org/10.1016/j.arr.2020.101045.

Guymer, R.H., Baird, P.N., Varsamidis, M., Busija, L., Dimitrov, P.N., Aung, K.Z., Makeyeva, G.A., Richardson, A.J., Lim, L., and Robman, L.D. (2013). Proof of concept, randomized, placebo-controlled study of the effect of simvastatin on the course of age-related macular degeneration. PloS one *8*, e83759. https://doi.org/10.1371/journal.pone.0083759.

Heesterbeek, T.J., Lorés-Motta, L., Hoyng, C.B., Lechanteur, Y.T.E., and Hollander, A.I. den (2020). Risk factors for progression of age-related macular degeneration. Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists) *40*, 140-170. https://doi.org/10.1111/opo.12675.

Holden, B., Sankaridurg, P., Smith, E., Aller, T., Jong, M., and He, M. (2014). Myopia, an underrated global challenge to vision: where the current data takes us on myopia control. Eye (London, England) *28*, 142-146. https://doi.org/10.1038/eye.2013.256.

Hopf, S., and Pfeiffer, N. (2017). Epidemiologie der Myopie. Der Ophthalmologe : Zeitschrift der Deutschen Ophthalmologischen Gesellschaft *114*, 20-23. https://doi.org/10.1007/s00347-016-0361-2.

Jaki Mekjavić, P., Jūratė Balčiūnienė, V., Ćeklić, L., Ernest, J., Jamrichova, Z., Zsolt Nagy, Z., Petkova, I., Teper, S., Gardašević Topčić, I., and Veith, M. (2019). The Burden of Macular Diseases in Central and Eastern Europe-Implications for Healthcare Systems. Value in health regional issues *19*, 1-6. https://doi.org/10.1016/j.vhri.2018.11.002.

Jarrett, S.G., and Boulton, M.E. (2012). Consequences of oxidative stress in age-related macular degeneration. Molecular aspects of medicine *33*, 399-417. https://doi.org/10.1016/j.mam.2012.03.009.

Jeong, S.-W., Kim, S.-H., Kang, S.-H., Kim, H.-J., Yoon, C.-H., Youn, T.-J., and Chae, I.-H. (2019). Mortality reduction with physical activity in patients with and without cardiovascular disease. European heart journal *40*, 3547-3555. https://doi.org/10.1093/eurheartj/ehz564.

Jones-Odeh, E., and Hammond, C.J. (2015). How strong is the relationship between glaucoma, the retinal nerve fibre layer, and neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis? Eye (London, England) *29*, 1270-1284. https://doi.org/10.1038/eye.2015.158.

Jorge, L., Canário, N., Quental, H., Bernardes, R., and Castelo-Branco, M. (2019). Is the Retina a Mirror of the Aging Brain? Aging of Neural Retina Layers and Primary Visual Cortex Across the Lifespan. Frontiers in aging neuroscience *11*, 360. https://doi.org/10.3389/fnagi.2019.00360.

Kaynak, S., Durak, I., Ozaksoy, D., and Canda, T. (1994). Restrictive myopic myopathy: computed tomography, magnetic resonance imaging, echography, and histological findings. The British journal of ophthalmology *78*, 414-415. https://doi.org/10.1136/bjo.78.5.414.

Kersten, E., Dammeier, S., Ajana, S., Groenewoud, J.M.M., Codrea, M., Klose, F., Lechanteur, Y.T., Fauser, S., Ueffing, M., and Delcourt, C., et al. (2019). Metabolomics in serum of patients with non-advanced age-related macular degeneration reveals aberrations in the glutamine pathway. PloS one *14*, e0218457. https://doi.org/10.1371/journal.pone.0218457.

Klein, R., Cruickshanks, K.J., Nash, S.D., Krantz, E.M., Nieto, F.J., Huang, G.H., Pankow, J.S., and Klein, B.E.K. (2010). The prevalence of age-related macular degeneration and associated risk factors. Archives of ophthalmology (Chicago, Ill. : 1960) *128*, 750-758. https://doi.org/10.1001/archophthalmol.2010.92.

Klein, R., and Klein, B.E.K. (2013). The prevalence of age-related eye diseases and visual impairment in aging: current estimates. Investigative ophthalmology & visual science *54*, ORSF5-ORSF13. https://doi.org/10.1167/iovs.13-12789.

Klein, R., Klein, B.E.K., Tomany, S.C., Danforth, L.G., and Cruickshanks, K.J. (2003). Relation of statin use to the 5-year incidence and progression of age-related maculopathy. Archives of ophthalmology (Chicago, Ill. : 1960) *121*, 1151-1155. https://doi.org/10.1001/archopht.121.8.1151.

Knudtson, M.D., Klein, R., and Klein, B.E.K. (2006). Physical activity and the 15-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. The British journal of ophthalmology *90*, 1461-1463. https://doi.org/10.1136/bjo.2006.103796.

Kolling, G. (1993). Zur Genese der Schielabweichung bei hoher Myopie. Klin Mbl Augenheilk.

Le Ma, Wang, Y., Du, J., Wang, M., Zhang, R., and Fu, Y. (2015). The association between statin use and risk of age-related macular degeneration. Scientific reports *5*, 18280. https://doi.org/10.1038/srep18280.

Lee, H., Jeon, H.L., Park, S.J., and Shin, J.Y. (2019). Effect of Statins, Metformin, Angiotensin-Converting Enzyme Inhibitors, and Angiotensin II Receptor Blockers on Age-Related Macular Degeneration. Yonsei medical journal *60*, 679-686. https://doi.org/10.3349/ymj.2019.60.7.679.

Li, J.Q., Welchowski, T., Schmid, M., Mauschitz, M.M., Holz, F.G., and Finger, R.P. (2020). Prevalence and incidence of age-related macular degeneration in Europe: a systematic review and meta-analysis. The British journal of ophthalmology *104*, 1077-1084. https://doi.org/10.1136/bjophthalmol-2019-314422.

Loprinzi, P.D., Swenor, B.K., and Ramulu, P.Y. (2015). Age-Related Macular Degeneration Is Associated with Less Physical Activity among US Adults: Cross-Sectional Study. PloS one *10*, e0125394. https://doi.org/10.1371/journal.pone.0125394.

MacMahon, B., and Pugh, T.F. (1970). Epidemiology: principles and methods (Little, Brown).

Maguire, M.G., Ying, G., McCannel, C.A., Liu, C., and Dai, Y. (2009). Statin use and the incidence of advanced age-related macular degeneration in the Complications of Age-related Macular Degeneration Prevention Trial. Ophthalmology *116*, 2381-2385. https://doi.org/10.1016/j.ophtha.2009.06.055.

Mahmood, S.S., Levy, D., Vasan, R.S., and Wang, T.J. (2014). The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet (London, England) *383*, 999-1008. https://doi.org/10.1016/S0140-6736(13)61752-3.

Mares, J.A., Voland, R.P., Sondel, S.A., Millen, A.E., Larowe, T., Moeller, S.M., Klein, M.L., Blodi, B.A., Chappell, R.J., and Tinker, L., et al. (2011). Healthy lifestyles related to subsequent prevalence of age-related macular degeneration. Archives of ophthalmology (Chicago, Ill. : 1960) *129*, 470-480. https://doi.org/10.1001/archophthalmol.2010.314.

Mauschitz, M.M. (2019). Ophthalmic assessments and retinal biomarkers in ageing and neurodegenerative diseases. The Rhineland Study.

Mauschitz, M.M., Bonnemaijer, P.W.M., Diers, K., Rauscher, F.G., Elze, T., Engel, C., Loeffler, M., Colijn, J.M., Ikram, M.A., and Vingerling, J.R., et al. (2018). Systemic and Ocular Determinants of Peripapillary Retinal Nerve Fiber Layer Thickness Measurements in the European Eye Epidemiology (E3) Population. Ophthalmology *125*, 1526-1536. https://doi.org/10.1016/j.ophtha.2018.03.026.

Mauschitz, M.M., and Finger, R.P. (2022). Age-Related Macular Degeneration and Cardiovascular Diseases: Revisiting the Common Soil Theory. Asia-Pacific journal of ophthalmology (Philadelphia, Pa.) *11*, 94-99. https://doi.org/10.1097/APO.0000000000000496.

Mauschitz, M.M., Holz, F.G., Finger, R.P., and Breteler, M.M.B. (2019a). Determinants of Macular Layers and Optic Disc Characteristics on SD-OCT: The Rhineland Study. Translational vision science & technology *8*, 34. https://doi.org/10.1167/tvst.8.3.34.

Mauschitz, M.M., Li, J.Q., Larsen, P.P., Köberlein-Neu, J., Holz, F.G., Breteler, M.M.B., and Finger, R.P. (2019b). Epidemiologie hochgradiger Sehbehinderungen und Blindheit älterer Menschen in

Deutschland. Der Ophthalmologe : Zeitschrift der Deutschen Ophthalmologischen Gesellschaft *116*, 201-212. https://doi.org/10.1007/s00347-019-0853-y.

Mauschitz, M.M., Schmitz, M.-T., Verzijden, T., Schmid, M., Thee, E.F., Colijn, J.M., Delcourt, C., Cougnard-Grégoire, A., Merle, B.M.J., and Korobelnik, J.-F., et al. (2022). Physical Activity, Incidence, and Progression of Age-Related Macular Degeneration: A Multicohort Study. American journal of ophthalmology *236*, 99-106. https://doi.org/10.1016/j.ajo.2021.10.008.

McGuinness, M.B., Finger, R.P., Karahalios, A., Guymer, R.H., English, D.R., Chong, E.W., Hodge, A.M., Robman, L.D., Giles, G.G., and Simpson, J.A. (2017a). Age-related macular degeneration and mortality: the Melbourne Collaborative Cohort Study. Eye (London, England) *31*, 1345-1357. https://doi.org/10.1038/eye.2017.139.

McGuinness, M.B., Karahalios, A., Simpson, J.A., Guymer, R.H., Robman, L.D., Hodge, A.M., Cerin, E., Giles, G.G., and Finger, R.P. (2016). Past physical activity and age-related macular degeneration: the Melbourne Collaborative Cohort Study. The British journal of ophthalmology *100*, 1353-1358. https://doi.org/10.1136/bjophthalmol-2015-307663.

McGuinness, M.B., Le, J., Mitchell, P., Gopinath, B., Cerin, E., Saksens, N.T.M., Schick, T., Hoyng, C.B., Guymer, R.H., and Finger, R.P. (2017b). Physical Activity and Age-related Macular Degeneration: A Systematic Literature Review and Meta-analysis. American journal of ophthalmology *180*, 29-38. https://doi.org/10.1016/j.ajo.2017.05.016.

McTaggart, F., and Jones, P. (2008). Effects of statins on high-density lipoproteins: a potential contribution to cardiovascular benefit. Cardiovascular drugs and therapy *22*, 321-338. https://doi.org/10.1007/s10557-008-6113-z.

Merle, B.M.J., Colijn, J.M., Cougnard-Grégoire, A., Koning-Backus, A.P.M. de, Delyfer, M.-N., Kiefte-de Jong, J.C., Meester-Smoor, M., Féart, C., Verzijden, T., and Samieri, C., et al. (2019). Mediterranean Diet and Incidence of Advanced Age-Related Macular Degeneration: The EYE-RISK Consortium. Ophthalmology *126*, 381-390. https://doi.org/10.1016/j.ophtha.2018.08.006.

Mitchell, P., Liew, G., Gopinath, B., and Wong, T.Y. (2018). Age-related macular degeneration. Lancet (London, England) *392*, 1147-1159. https://doi.org/10.1016/S0140-6736(18)31550-2.

Mok, A., Khaw, K.-T., Luben, R., Wareham, N., and Brage, S. (2019). Physical activity trajectories and mortality: population based cohort study. BMJ (Clinical research ed.) *365*, l2323. https://doi.org/10.1136/bmj.l2323.

Munch, I.C., Linneberg, A., and Larsen, M. (2013). Precursors of age-related macular degeneration: associations with physical activity, obesity, and serum lipids in the inter99 eye study. Investigative ophthalmology & visual science *54*, 3932-3940. https://doi.org/10.1167/iovs.12-10785.

Mury, P., Chirico, E.N., Mura, M., Millon, A., Canet-Soulas, E., and Pialoux, V. (2018). Oxidative Stress and Inflammation, Key Targets of Atherosclerotic Plaque Progression and Vulnerability: Potential Impact of Physical Activity. Sports medicine (Auckland, N.Z.) *48*, 2725-2741. https://doi.org/10.1007/s40279-018-0996-z.

Mutlu, U., Bonnemaijer, P.W.M., Ikram, M.A., Colijn, J.M., Cremers, L.G.M., Buitendijk, G.H.S., Vingerling, J.R., Niessen, W.J., Vernooij, M.W., and Klaver, C.C.W., et al. (2017). Retinal neurodegeneration and brain MRI markers: the Rotterdam Study. Neurobiology of aging *60*, 183-191. https://doi.org/10.1016/j.neurobiolaging.2017.09.003.

Mutlu, U., Colijn, J.M., Ikram, M.A., Bonnemaijer, P.W.M., Licher, S., Wolters, F.J., Tiemeier, H., Koudstaal, P.J., Klaver, C.C.W., and Ikram, M.K. (2018a). Association of Retinal Neurodegeneration on

Optical Coherence Tomography With Dementia: A Population-Based Study. JAMA neurology *75*, 1256-1263. https://doi.org/10.1001/jamaneurol.2018.1563.

Mutlu, U., Ikram, M.K., Roshchupkin, G.V., Bonnemaijer, P.W.M., Colijn, J.M., Vingerling, J.R., Niessen, W.J., Ikram, M.A., Klaver, C.C.W., and Vernooij, M.W. (2018b). Thinner retinal layers are associated with changes in the visual pathway: A population-based study. Human brain mapping *39*, 4290-4301. https://doi.org/10.1002/hbm.24246.

Olshan, A.F., Diez Roux, A.V., Hatch, M., and Klebanoff, M.A. (2019). Epidemiology: Back to the Future. American journal of epidemiology *188*, 814-817. https://doi.org/10.1093/aje/kwz045.

Ong, Y.-T., Hilal, S., Cheung, C.Y., Venketasubramanian, N., Niessen, W.J., Vrooman, H., Anuar, A.R., Chew, M., Chen, C., and Wong, T.Y., et al. (2015). Retinal neurodegeneration on optical coherence tomography and cerebral atrophy. Neuroscience letters *584*, 12-16. https://doi.org/10.1016/j.neulet.2014.10.010.

Patterson, C. (2018). World Alzheimer Report 2018. The state of the art of dementia research: New frontiers.

Ranka, M.P., and Steele, M.A. (2015). Esotropia associated with high myopia. Current opinion in ophthalmology *26*, 362-365. https://doi.org/10.1097/ICU.0000000000000180.

Reuter, S., Gupta, S.C., Chaturvedi, M.M., and Aggarwal, B.B. (2010). Oxidative stress, inflammation, and cancer: how are they linked? Free radical biology & medicine *49*, 1603-1616. https://doi.org/10.1016/j.freeradbiomed.2010.09.006.

Roizenblatt, M., Naranjit, N., Maia, M., and Gehlbach, P.L. (2018). The Question of a Role for Statins in Age-Related Macular Degeneration. International journal of molecular sciences *19*. https://doi.org/10.3390/ijms19113688.

Romdhoniyyah, D.F., Harding, S.P., Cheyne, C.P., and Beare, N.A.V. (2021). Metformin, A Potential Role in Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis. Ophthalmology and therapy *10*, 245-260. https://doi.org/10.1007/s40123-021-00344-3.

Rothman, K.J. (2007a). Commentary: Epidemiology still ascendant. International journal of epidemiology *36*, 710-711. https://doi.org/10.1093/ije/dym151.

Rothman, K.J. (2007b). Real world data. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research *10*, 322-323. https://doi.org/10.1111/j.1524-4733.2007.00277.x.

Rothman, K.J. (2012). Epidemiology: An Introduction. 2nd Edition (Oxford: Oxford University Press).

Schnabolk, G. (2019). Systemic Inflammatory Disease and AMD Comorbidity. Advances in experimental medicine and biology *1185*, 27-31. https://doi.org/10.1007/978-3-030-27378-1_5.

Schwabe, U., and Ludwig, W.-D.L. (2020). Arzneiverordnungs-Report 2020 (Springer).

Spaide, R.F., Jaffe, G.J., Sarraf, D., Freund, K.B., Sadda, S.R., Staurenghi, G., Waheed, N.K., Chakravarthy, U., Rosenfeld, P.J., and Holz, F.G., et al. (2020). Consensus Nomenclature for Reporting Neovascular Age-Related Macular Degeneration Data: Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group. Ophthalmology *127*, 616-636. https://doi.org/10.1016/j.ophtha.2019.11.004.

Stark, C.R., and Mantel, N. (1966). Effects of maternal age and birth order on the risk of mongolism and leukemia. Journal of the National Cancer Institute *37*, 687-698.

Stewart, J.M., Lamy, R., Wu, F., and Keenan, J.D. (2020). Relationship between Oral Metformin Use and Age-Related Macular Degeneration. Ophthalmology. Retina *4*, 1118-1119. https://doi.org/10.1016/j.oret.2020.06.003.

Su, Y., Shen, Q., and Fan, X. (2016). Loop Myopexy Surgery for Strabismus Associated with High Myopia. Journal of ophthalmology *2016*, 8657036. https://doi.org/10.1155/2016/8657036.

Sung, M.S., Choi, S.-M., Kim, J., Ha, J.Y., Kim, B.-C., Heo, H., and Park, S.W. (2019). Inner retinal thinning as a biomarker for cognitive impairment in de novo Parkinson's disease. Scientific reports *9*, 11832. https://doi.org/10.1038/s41598-019-48388-7.

Szklo, M. (1998). Population-based cohort studies. Epidemiologic reviews *20*, 81-90. https://doi.org/10.1093/oxfordjournals.epirev.a017974.

Tabatabaei-Jafari, H., Shaw, M.E., and Cherbuin, N. (2015). Cerebral atrophy in mild cognitive impairment: A systematic review with meta-analysis. Alzheimer's & dementia (Amsterdam, Netherlands) *1*, 487-504. https://doi.org/10.1016/j.dadm.2015.11.002.

Uchida, A., Pillai, J.A., Bermel, R., Jones, S.E., Fernandez, H., Leverenz, J.B., Srivastava, S.K., and Ehlers, J.P. (2020). Correlation between brain volume and retinal photoreceptor outer segment volume in normal aging and neurodegenerative diseases. PloS one *15*, e0237078. https://doi.org/10.1371/journal.pone.0237078.

United Nations, Department of Economic and Social Affairs (2017). , Population Division. World Population Prospects: The 2017 Revision, Key Findings and Advance (New York).

VanderBeek, B.L., Zacks, D.N., Talwar, N., Nan, B., and Stein, J.D. (2013). Role of statins in the development and progression of age-related macular degeneration. Retina (Philadelphia, Pa.) *33*, 414-422. https://doi.org/10.1097/IAE.0b013e318276e0cf.

Vinores, S.A. (1995). Assessment of blood-retinal barrier integrity. Histology and histopathology *10*, 141-154.

Warburton, D.E.R., and Bredin, S.S.D. (2017). Health benefits of physical activity: a systematic review of current systematic reviews. Current opinion in cardiology *32*, 541-556. https://doi.org/10.1097/HCO.0000000000000437.

Ward, D.D., Mauschitz, M.M., Bönniger, M.M., Merten, N., Finger, R.P., and Breteler, M.M.B. (2020). Association of retinal layer measurements and adult cognitive function: A population-based study. Neurology *95*, e1144-e1152. https://doi.org/10.1212/WNL.0000000000010146.

Wen, C.P., Wai, J.P.M., Tsai, M.K., Yang, Y.C., Cheng, T.Y.D., Lee, M.-C., Chan, H.T., Tsao, C.K., Tsai, S.P., and Wu, X. (2011). Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet (London, England) *378*, 1244-1253. https://doi.org/10.1016/S0140-6736(11)60749-6.

Wong, W.L., Su, X., Li, X., Cheung, C.M.G., Klein, R., Cheng, C.-Y., and Wong, T.Y. (2014). Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. The Lancet. Global health *2*, e106-16. https://doi.org/10.1016/S2214-109X(13)70145-1.

World Health Organization (2019). World report on vision 2019 (Geneva).

World Health Organization (2020). WHO guidelines on physical activity and sedentary behaviour. Licence: CC BY-NC-SA 3.0 IGO.

Wu, P.-C., Huang, H.-M., Yu, H.-J., Fang, P.-C., and Chen, C.-T. (2016). Epidemiology of Myopia. Asia-Pacific journal of ophthalmology (Philadelphia, Pa.) *5*, 386-393. https://doi.org/10.1097/APO.0000000000000236.

Yamaguchi, M., Yokoyama, T., and Shiraki, K. (2010). Surgical procedure for correcting globe dislocation in highly myopic strabismus. American journal of ophthalmology *149*, 341-346.e2. https://doi.org/10.1016/j.ajo.2009.08.035.

Yokoyama, T., Tabuchi, H., Ataka, S., Shiraki, K., Miki, T., and Mochizuki, K. (2000). The mechanism of development in progressive esotropia with high myopia. Jan-Tjeerd de Faber. Transactions 26th Meeting of the European Strabismological Association, 218-221.