Association of lipid-lowering drugs and anti-diabetic drugs with age-related macular degeneration: A meta-analysis in Europeans

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Synopsis/Precis: Systemic use of lipid-lowering drugs and antidiabetic drug is associated with lower prevalence of AMD across multiple European cohorts.

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- and hospital-based studies from the European Eye Epidemiology (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.

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% 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.

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 etiology 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 (LLD) and anti-diabetic 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 co-morbidities 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.[1, 2] In Europe, 67 million 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 patho-etiogenetic 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 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 anti-diabetic 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 E3 population.

METHODS

Included Studies

The European Eye Epidemiology (E3) consortium is a collaborative network across Europe with the overarching aim of developing and analyzing 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 United Kingdom (Table1). Data from seven included studies from the EYERISK project (Alienor (Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires) - Study, Crescendo-3C Study, MARS (Muenster Aging and Retina Study), Montrachet Study, PAMDI (Prevalence of Age-Related Macular Degeneration in Italy) - Study, Thessaloniki Eye Study, and Tromsø Eye Study) were harmonized in advance as described previously.[7]
The other seven included studies were the AugUR (Age-related diseases: understanding genetic and non-genetic influences - a study at the University of Regensburg) - Study[34], the Coimbra Eye Study (CES)[35], the EPIC-Norfolk (European Prospective Investigation into Cancer-Norfolk) - Study[36], the Gutenberg Health Study (GHS)[37], the LIFE (Leipzig Research Centre for Civilization Diseases) -Adult Study (LIFE-Adult)[38], the NICOLA (Northern Ireland Cohort for the Longitudinal Study of Ageing) - Study[39], and the UEMS (Ural Eye and Medical study).[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 age-related macular degeneration

AMD was graded on color 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, i.e. geographic atrophy (GA) and macular neovascularization (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 standardized 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), anti-diabetic 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 anti-diabetic drugs were not adjusted for prevalent diabetes). Co-variables 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 harmonized 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 odds ratios (OR) with 95% confidence intervals (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 co-variables 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 (version 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 anti-diabetic drugs to be associated with lower AMD prevalence in both the basic model 1 (supplemental figures 1

and 2) and the fully adjusted model 2 (OR 0.85; 95% CI 0.79 - 0.91; p<0.001, I^2=0%; and OR 0.78; 95% CI 0.66 - 0.91, p=0.002, I^2=57%, respectively; Figures 1 and 2). We observed no association of LLD and anti-diabetic drugs with late AMD (OR 0.87; 95% CI 0.71 - 1.06; p=0.16, I^2=0%; and OR 1.12; 95% CI 0.87 - 1.44, p=0.37, I^2=0%, for model 2 respectively; supplemental figures 3 and 4) and no association of NSAID and L-dopa with any form of AMD (supplemental figures 5-8). Additional sensitivity analyses, excluding LIFE-Adult data, showed similar results (data not shown).

1 **Table 1**. Characteristic of included studies.

Study		n	Age (mean ± SD)	Women (%)	AMD (%)						Systemic use (%)			
					No		Early		Late		NSAID	LLD	Anti-diabetics	L-Dopa
					n	%	n	%	n	%				
EYE RISK *	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%

AMD=Age-related macular degeneration; NSAID= non-steroidal anti-inflammatory drugs; LLD=Lipid-lowering drugs; Tromsø= Tromsø Eye Study; Thessaloniki= Thessaloniki Eye Study; Montrachet= Montrachet Study; MARS=Muenster Aging and Retina Study; Alienor= Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires; PAMDI= Prevalence of Age-Related Macular Degeneration in Italy Study; Crescendo-3C= Crescendo-3C Study; GHS=Gutenberg Health Study; EPIC-Norfolk= European Prospective Investigation into Cancer-Norfolk-Study; LIFE-Adult= (Leipzig Research Centre for Civilization Diseases)-Adult Study; UEMS= Ural Eye and Medical study; NICOLA= Northern Ireland Cohort for the Longitudinal Study of Ageing; AugUR= Age-related diseases: understanding genetic and non-genetic influences - a study at the University of Regensburg; CES=Coimbra Eye Study;
*Participants below the age of 50 years were excluded in this analysis; NA=data not available;
[P]=Population-based study; [C]=Case-control Study
Characteristics based on participants with available data on AMD, age and sex and at least one medication; sample size of model2 is smaller due to missing data on co-variables

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DISCUSSION

Our study indicates an association of systemic use of LLD and anti-diabetic 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 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-analyzing individual level data from various population- and hospital-based studies instead of meta-analyzing 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 (LDL) and cholesterol, various LLD have been reported to have anti-inflammatory and anti-oxidant 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 randomized 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 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 anti-diabetic 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 hypothesized 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 aging. Metformin is considered to have anti-oxidative 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 adenosine triphosphate (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 (COX-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 a randomized controlled trial (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 anti-thrombotic 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 (GPR143) 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 color fundus photography in all studies using very similar and comparable classification systems. Image grading protocols differed slightly between studies but were either harmonized 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. Firstly, 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 (e.g. LLD included statins and fibrates, and anti-diabetic 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 pre- clinical 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 (OCT) 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 anti-diabetic drugs do prolong the lifespan. Thus, late AMD cases may have died before enrollment in our studies. In contrast, some participants may also contribute to an indication bias; i.e. individuals using these drugs are in worse general health

and hence, given that AMD and cardiovascular disease (CVD) have been shown to be associated[71], our detected associations may even be underestimated. A potential co-morbidity of AMD with metabolic diseases such as diabetes and hyperlipidemia may have contributed to the detected effects. The relation of diabetes and hyperlipidemia 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 hyperlipidemia (where data was available) and found no systematic bias in either direction (supplemental table 1). Moreover, it is important to note that participants with diabetes and hyperlipidemia were on average older and thus more likely to have AMD. Lastly, a potential synergistic effect of further drugs (e.g. anti-hypertensive 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 generalizable to other populations.[10]

In conclusion, our study suggests that regular intake of LLD and anti-diabetic 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 etiology. Further longitudinal studies are needed to confirm or refute these associations.

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Ethics statement:

This study involves human participants but was not approved by an Ethics Committee(s) or Institutional Board(s):

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). Permission to access and use the data was obtained from all studies.

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Figure1. Forest plot of meta-analyzed associations of lipid-lowering drugs with prevalent AMD (model 2; n= 30,449, I^2 heterogeneity=0%; RE=random-effects).

Figure 2. Forest plot of meta-analyzed associations of anti-diabetic drugs with prevalent AMD (model 2; n=33,874; I^2 heterogeneity=57%; RE=random-effects).