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

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

3
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75

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79

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

82

83

84 **Abstract**

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

87 **Methods:** We included 38,694 adults from 14 population- and hospital-based studies from
88 the European Eye Epidemiology (E3) consortium. We examined associations between the
89 use of systemic medications and any prevalent AMD as well as any late AMD using
90 multivariable logistic regression modelling per study and pooled results using random effects
91 meta-analysis.

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

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

101
102
103

104 **What is already known on this topic**

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

108

109

110 **What this study adds**

111 This is the first large-scale study showing an association of using lipid-lowering drugs (LLD)
112 and anti-diabetic drugs with lower AMD prevalence in the general population using data from
113 multiple European cohort studies.

114

115

116 **How this study might affect research, practice or policy**

117 These findings have implications for public health messages, underline the link of AMD with
118 cardiovascular co-morbidities and may provide potential future therapeutic targets.

119

120 **INTRODUCTION**

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

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

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

133 Despite decades of research, we still lack therapeutic measures and interventions to prevent
134 AMD or slow down progression[10, 12, 15], underscoring the need for better understanding
135 and novel prevention or therapeutic strategies. Previous studies investigated the relation of
136 AMD and different systemic medications, which interfere with pathways that also play a role
137 in AMD pathogenesis and hence may affect it. These include lipid-lowering drugs (LLD)[16]
138 for the lipid metabolism and lipid accumulation, non-steroidal anti-inflammatory drugs
139 (NSAID)[17–19] and anti-diabetic drugs (particularly metformin)[20, 21], which may reduce
140 inflammation and oxidative stress, and levodopa (L-Dopa)[22], which was reported to
141 upregulate the retinal pigment epithelium (RPE) metabolism. Metformin and LLD rank among
142 the top prescribed drugs in Germany, Europe and the USA[23, 24], while NSAID are some of
143 the most frequently used over-the-counter (OTC) drugs[25]. Results of studies to date,
144 however, have been inconsistent, based on small sample size or used self-reported AMD as
145 outcome.[16, 26–32] Thus, it remains unclear as to whether any of these drugs are
146 associated with AMD.

147 Hence, we aimed to explore associations between the use of aforementioned medications
148 and presence of AMD in the E3 population.

149

150 **METHODS**

151 *Included Studies*

152 The European Eye Epidemiology (E3) consortium is a collaborative network across Europe
153 with the overarching aim of developing and analyzing large pooled datasets to increase
154 understanding of eye diseases and vision loss.[33] For this meta-analysis, we included **14**
155 population or hospital-based E3 studies with available data on systemic medication use and
156 AMD from France, Germany, Greece, Ireland, Italy, Norway, Portugal, Russia, and the
157 United Kingdom (Table1). Data from seven included studies from the EYERISK project
158 (Alienor (Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires) - Study,
159 Crescendo-3C Study, MARS (Muenster Aging and Retina Study), Montrachet Study, PAMDI
160 (Prevalence of Age-Related Macular Degeneration in Italy) - Study, Thessaloniki Eye Study,
161 and Tromsø Eye Study) were harmonized in advance as described previously.[7]

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

172

173 *Grading of age-related macular degeneration*

174 AMD was graded on color fundus photographs according to the Wisconsin age-related
175 maculopathy grading system (WARMGS).[41] The worse eye determined the overall AMD
176 status using the Rotterdam classification[42] in the EYERISK studies, the CES, the GHS,
177 and LIFE-Adult[43], the Beckmann initiative clinical classification of AMD in AugUR, NICOLA,
178 and UEMS[44] and a modified WARMGS protocol in EPIC-Norfolk.[36]
179 The classification of late AMD, i.e. geographic atrophy (GA) and macular neovascularization
180 (MNV), was consistent across all studies, whereas the definition of early and intermediate
181 AMD differed between studies. To overcome this heterogeneity, we assessed the presence
182 of both “any AMD” and of “late AMD”.

183

184 *Medication assessments*

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

191

192 *Statistical Analysis*

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

202 Subsequently, we performed random-effects meta-analysis to combine effect estimates
203 presented as odds ratios (OR) with 95% confidence intervals (95% CI) of each medication
204 from the multivariable models among studies. A random-effects approach was chosen a
205 priori on the basis of the heterogeneity of study participants and the design of the studies.[45]
206 As further analysis, we repeated all logistic regression models with prevalent late AMD as
207 dependent variable.
208 Not all studies held information on all medications or co-variables and within UEMS smoking
209 status only distinguished current smokers from non-smokers, which included former
210 smokers. In the event that studies were unable to provide a model due to a missing
211 exposure, that study was excluded from the respective model. Moreover, we excluded EPIC-
212 Norfolk from all and CES, NICOLA, and GHS from some models of late AMD, because there
213 were too few cases (either of late AMD or medication use), that did not allow for robust
214 statistical modelling. Given that the LIFE-Adult only had data on prevalence of early AMD, we
215 repeated the meta-analysis without LIFE-Adult data as a sensitivity analysis. All analyses
216 were performed with the statistical software RStudio (version 4.0.2, R Core Team (2021). R:
217 A language and environment for statistical computing. R Foundation for Statistical
218 Computing, Vienna, Austria. URL: <https://www.R-project.org/>) with the add-on package
219 metafor.

220

221 **RESULTS**

222 Mean age of 38,694 participants (with available data on AMD, age, sex, and at least one
223 medication) ranged from 61.5 ± 7.1 years in the GHS to 82.6 ± 3.8 years in the Crescendo-
224 3C Study. Prevalence of any AMD ranged from 12.1% in the GHS to 64.5% in MARS and
225 prevalence of late AMD ranged from 0.5% in the EPIC-Norfolk Study to 35.5% in MARS, with
226 9332 and 951 cases for any and late AMD, respectively. Table 1 presents further population
227 characteristics and use of systemic medications.

228 In our random-effects meta-analysis, we found LLD intake and use of anti-diabetic drugs to
229 be associated with lower AMD prevalence in both the basic model 1 (supplemental figures 1

230 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
231 0.78; 95% CI 0.66 - 0.91, $p = 0.002$, $I^2 = 57\%$, respectively; Figures 1 and 2). We observed no
232 association of LLD and anti-diabetic drugs with late AMD (OR 0.87; 95% CI 0.71 - 1.06;
233 $p = 0.16$, $I^2 = 0\%$; and OR 1.12; 95% CI 0.87 - 1.44, $p = 0.37$, $I^2 = 0\%$, for model 2 respectively;
234 supplemental figures 3 and 4) and no association of NSAID and L-dopa with any form of
235 AMD (supplemental figures 5-8). Additional sensitivity analyses, excluding LIFE-Adult data,
236 showed similar results (data not shown).

237 **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

239 **DISCUSSION**

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

245 One of the first studies on the impact of statins on AMD used longitudinal data of 2780
246 participants and could not find an association of LLD with AMD incidence or progression.[27]
247 Subsequently, several cross-sectional and longitudinal studies of different sample size
248 investigated this relationship and reported inconsistent results.[46] While some studies
249 reported possibly beneficial impact of statins on cross-sectional AMD prevalence[32] and
250 progression over time[26, 29, 47], other studies, both cross-sectional and longitudinal, did not
251 find any associations[30, 31, 48–52] or even suggested an increased risk for neovascular
252 AMD.[28] One recent review maintains the potentially beneficial role of statins in AMD while
253 underscoring the complexity of underlying associations,[53] , while two others could not
254 confirm an association.[54, 55] Our study supports the body of evidence suggesting a
255 beneficial association with AMD and represents, to our knowledge, the first study meta-
256 analyzing individual level data from various population- and hospital-based studies instead of
257 meta-analyzing published aggregated results only. Yet, further longitudinal data are needed
258 to confirm our findings, which are inherently limited by using cross-sectional data only and
259 cannot infer causality. Apart from lowering serum levels of low-density lipoprotein (LDL) and
260 cholesterol, various LLD have been reported to have anti-inflammatory and anti-oxidant
261 effects, which also play a role in AMD pathogenesis.[6, 9, 16] However, even though the
262 beneficial impact of LLD on AMD seems biologically plausible, support for this assertion in
263 longitudinal studies would strengthen the evidence. Earlier randomized controlled trials
264 (RCT) failed to show a causal relation[48, 49], likely due to the multifactorial nature of the
265 disease, small sample size and limited follow-up. Interestingly, several studies reported an
266 association of higher levels of high-density lipoprotein (HDL) and specific subclasses such as

267 HDL-C with an increased risk of AMD. [12, 56, 57] This opposes the generally beneficial role
268 of HDL in cardiovascular disease and underscores the complexity and need for further
269 intensive research. Particularly, given that statins have been reported to increase serum
270 levels of HDL-C, which would conflict our results of an association of lower AMD prevalence
271 in statin use. [58, 59]

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

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

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

306 We also found no association of L-dopa use and AMD in our data. Few previous studies
307 reported L-dopa to affect a G protein-coupled receptor (GPR143) on the RPE increasing its
308 metabolism and suggested L-dopa as beneficial drug for treatment of AMD with less incident
309 AMD and later onset as well as fewer needed intravitreal injections in exudative late AMD
310 using longitudinal data.[22, 70] This drug, however, is not frequently used in the general
311 population and hence the absence of any association of L-dopa in our population is likely due
312 to being statistically underpowered.

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

321 However, several limitations need to be considered. Firstly, our study included cross-
322 sectional data only. Thus, our findings display statistical association between drug use and
323 AMD prevalence only and do not allow for the assessment of causality or risk. Assessments
324 of systemic medication intake differed between studies and may be subject to re-call bias,
325 misclassification or incomplete records. Moreover, duration of intake was not
326 comprehensively assessed and we combined classes of drugs and did not differentiate
327 between specific subtypes (e.g. LLD included statins and fibrates, and anti-diabetic drugs
328 included oral drugs and insulin). Lastly, the prescription of any medication does not confirm
329 the actual intake, which would be better represented by blood levels of the specific agent.
330 These methodological differences may have introduced noise, reduced statistical precision
331 and did not allow for assessments of drug-dose-relationship. As expected, when combining
332 different large-scale (population) studies, we observed between-study heterogeneity for
333 different variables, which was addressed by using random-effect meta-analysis. Moreover,
334 LIFE-Adult only provided data on early AMD, different to all other studies. Therefore, we
335 performed a sensitivity analysis excluding LIFE-Adult which did not change the results (data
336 not shown). Moreover, variation in the classification of early and pre-clinical stages of AMD
337 between studies may have created noise in the data and reduced statistical power. In
338 contrast to small clinical studies, our large-scale population studies did not have detailed
339 information on disease severity, duration and variance of serum levels of glucose or lipids,
340 which may provide more insight in underlying mechanisms.

341 The absence of detected associations with late AMD is likely due to a lack of statistical power
342 caused by too few cases. Yet, AMD classification was based on fundus photography only. A
343 multimodal approach including optical coherence tomography (OCT) may have been more
344 sensitive for subtle cases of late, particularly neovascular, AMD. Moreover, our population
345 may underlie a potential survival bias of healthier participants or participants in which intake
346 of drugs such as LLD and anti-diabetic drugs do prolong the lifespan. Thus, late AMD cases
347 may have died before enrollment in our studies. In contrast, some participants may also
348 contribute to an indication bias; i.e. individuals using these drugs are in worse general health

349 and hence, given that AMD and cardiovascular disease (CVD) have been shown to be
350 associated[71], our detected associations may even be underestimated. A potential co-
351 morbidity of AMD with metabolic diseases such as diabetes and hyperlipidemia may have
352 contributed to the detected effects. The relation of diabetes and hyperlipidemia with AMD is
353 yet to be clarified and previous studies reported contradictive results [72–74]. In addition,
354 there may have been a potential misclassification of AMD in few cases of severe diabetic
355 retinopathy, which, again, could have introduced more noise into the data. We performed a
356 sensitivity analysis stratifying AMD prevalence by disease status of diabetes and
357 hyperlipidemia (where data was available) and found no systematic bias in either direction
358 (supplemental table 1). Moreover, it is important to note that participants with diabetes and
359 hyperlipidemia were on average older and thus more likely to have AMD. Lastly, a potential
360 synergistic effect of further drugs (e.g. anti-hypertensive drugs) may have contributed to our
361 results. We did adjust our models for prevalent hypertension, but residual confounding may
362 be present. The combination of potential noise within medication and AMD data, the
363 heterogeneity between studies and a possible selection bias of more healthy participants in
364 large-scale (population) studies, may have reduced our statistical power and led to
365 potentially underestimating detected associations. Lastly, all studies were mostly of
366 Caucasian ethnicity and results may not be generalizable to other populations.[10]
367 In conclusion, our study suggests that regular intake of LLD and anti-diabetic drugs is
368 associated with reduced prevalence of AMD in the general population. Given a potential
369 interference of these drugs with pathophysiological pathways relevant in AMD, this may
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372

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432 This study involves human participants but was not approved by an Ethics Committee(s) or
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434 This current study is based on previously assessed granular data from 14 studies. Therefore,
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436 tenets of the Declaration of Helsinki and had local ethical committee approval (see key
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441

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Figure 1. 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).