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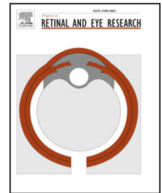
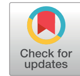


A new perspective on lipid research in age-related macular degeneration



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ABSTRACT

There is an urgency to find new treatment strategies that could prevent or delay the onset or progression of AMD. Different classes of lipids and lipoproteins metabolism genes have been associated with AMD in a multiple ways, but despite the ever-increasing knowledge base, we still do not understand fully how circulating lipids or local lipid metabolism contribute to AMD. It is essential to clarify whether dietary lipids, systemic or local lipoprotein metabolismtrafficking of lipids in the retina should be targeted in the disease. In this article, we critically evaluate what has been reported in the literature and identify new directions needed to bring about a significant advance in our understanding of the role for lipids in AMD. This may help to develop potential new treatment strategies through targeting the lipid homeostasis.

1. Introduction

Age-related macular degeneration (AMD) is a progressive retinal disease and is the leading cause of visual impairment in elderly in western countries, for which there is still no cure (Bourne et al., 2013; Lim et al., 2012). AMD is etiologically complex, meaning it has many environmental, behavioural, and genetic factors that influence susceptibility to the development of the disease (DeAngelis et al., 2017; Fritsche et al., 2014; Lim et al., 2012).

Early stages of AMD are characterized by deposits of extracellular

Abbreviations: ABCA1, ATP binding cassette subfamily A member 1; AMD, age-related macular degeneration; APOA1, Apolipoprotein A-I; APOE, Apolipoprotein E; APOB, Apolipoprotein B; AREDS, Age-Related Eye Disease Study; C3, Complement component 3; C9, Complement component 9; CD36, cluster of differentiation 36; CETP, cholesteryl ester transfer protein; CFH, Complement Factor H; CI, confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, Eicosapentaenoic acid; FBS, fetal bovine serum; GA, geographic atrophy; GWAS, genome-wide association study; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HMGR, 3-hydroxy-3-methylglutary coenzyme A reductase; iPSC, Induced Pluripotent Stem Cells; LC-PUFA, Long-chain polyunsaturated fatty acid; LCAT, lecithin-cholesterol acyltransferase; LDL-C, low-density lipoprotein cholesterol; LIPC, Lipase C; Lipoprotein(a), Lp(a); MUFA, Monounsaturated Fatty Acid; NAT-2, Nutritional AMD Treatment 2; OR, odds ratio; RPE, retinal pigment epithelium; RBCM, Red-blood cells membranes; RCTs, randomized controlled trials; SFA, saturated fatty acids; SR-BI, scavenger receptor class B type I; SR-BII, scavenger receptor class B type II; SREBPs, sterol regulatory element-binding proteins; TC, total cholesterol; TG, triglycerides; VEGF, vascular endothelial growth factor; VLDL, very low-density lipoprotein

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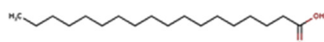
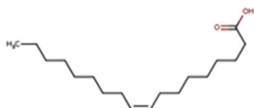
Saturated Fatty Acids (SFA)



e.g. Stearic acid (SA), C18

Monounsaturated Fatty Acids (MUFAs)



e.g. Oleic acid (OA), C18:1

Polyunsaturated Fatty Acids (PUFAs)

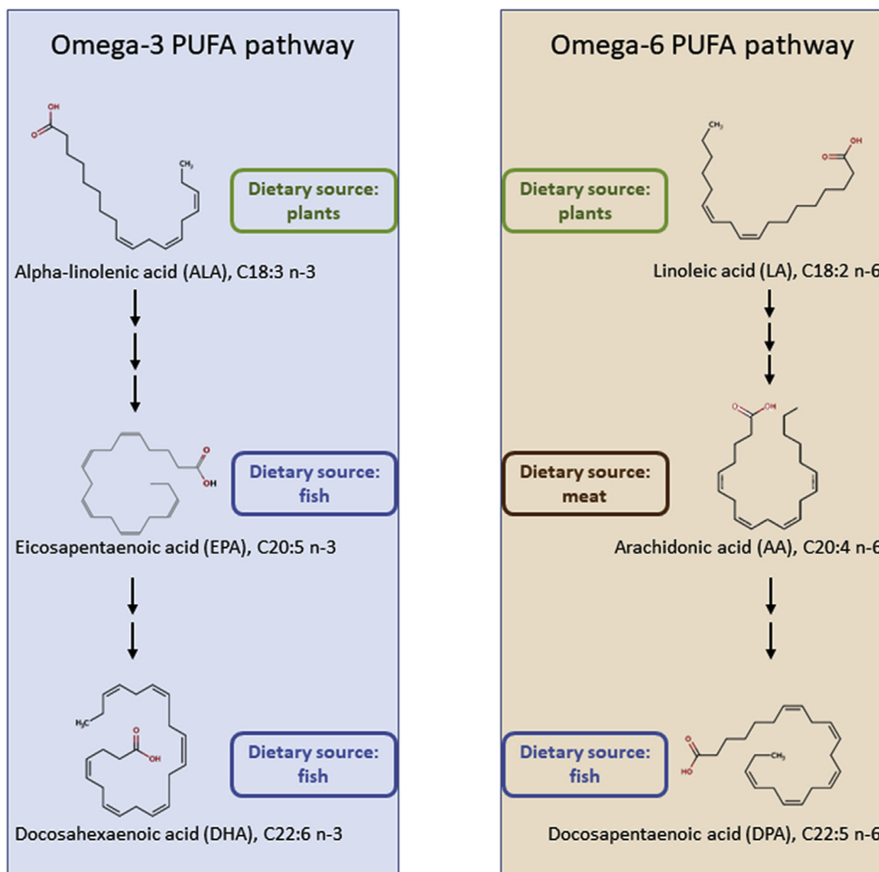


Fig. 1. Biochemical structure for fatty acids and biochemical pathway for the interconversion of omega-6 and omega-3 fatty acids.

material at both the apical and basal aspects of the retinal pigment epithelium (RPE). Deposits at the basal aspect of RPE are hallmarks of AMD and are best understood. Closest to the RPE cell bodies is basal laminar deposit, a diffusely distributed extracellular material between the RPE basal lamina and its plasma membrane. Between the RPE basal lamina and the inner collagenous layer of Bruch's membrane (sub-RPE-basal lamina space) (Balaratnasingam et al., 2016) are basal linear deposit and drusen, which are diffuse and focal forms of deposit that are rich in proteins, lipids and minerals (Curcio and Millican, 1999; Green and Enger, 1993; Sarks et al., 1988). Much less well understood are deposits between the apical surface of the RPE and the photoreceptors (subretinal drusenoid deposits, also called reticular pseudodrusen). Intermediate AMD is characterized by drusen of diameter ≥125 μm and signs of RPE pigmentary abnormalities (Ferris et al., 2013). AMD has two clinical end-stages: (1) atrophic/dry form, which is called geographic atrophy (GA) of the RPE when diagnosed by color fundus photography and complete RPE and outer retinal atrophy when diagnosed by optical coherent tomography (Ferris et al., 2013), and (2) neovascular form, whereby choroidal vessels penetrate the Bruch's membrane, or retinal vessels penetrate the RPE, both ramifying in the sub-RPE-basal laminar space and/or subretinal space and causing hemorrhage or the buildup of fluid in the two spaces, and eventually leading to scarring if untreated.

The introduction of anti-vascular endothelial growth factor (VEGF) injections revolutionized the treatment of neovascularisation in the past 10 years (Chakravarthy et al., 2013). Despite the huge success of anti-VEGF therapy, this treatment is not curative, only extends the period before patients lose their central vision, often due to the development of GA (Grunwald et al., 2014). Moreover, there is currently no treatment for GA. Therefore, it remains a necessity to find new interventions, if possible at an early stage, before irreversible changes take place. A growing body of evidence suggests that lipids play a pivotal role in the development of AMD. Epidemiological studies on dietary lipids, measurements of circulating lipoproteins, genome-wide association studies

(GWASs) and studies on model systems implicate lipids at different stages of AMD. Therefore, this review focuses on the role of lipids in various aspects of AMD pathology, ranging from diet to genetic risk variants, lipoproteins metabolism in the retina and the use of model systems for retinal lipid homeostasis as well as the interaction of lipids with other pathways. We explore how a better understanding of the role lipids play in the development and maintenance of disease processes could help to develop new treatment options for AMD.

2. Dietary fatty acids and AMD

Nutritional factors contribute to the development of AMD. Nutrients with antioxidant properties, such as lutein and zeaxanthin, vitamin C, E and zinc, and fatty acids such as omega-3 long-chain polyunsaturated fatty acids (omega-3 LC-PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may help reduce the risk for AMD (Lim et al., 2012).

Fatty acids consist of a hydrocarbon chain, a carboxyl group and a methyl group at each of their ends. Fatty acids have different functions in our body including storage as triglycerides (3 fatty acids connected to a glycerol) to be used as energy substrate; major constituents of the lipidic bilayer of cell membranes; participating to the cholesterol esters formation. Fatty acids are characterized by their number of carbon and double bonds. Saturated fatty acids (SFAs) have no double bond, monounsaturated fatty acids (MUFAs) have one, and PUFAs have two or more. PUFAs are divided into two families: omega-3 and omega-6 depending on whether the first double bond is located at the 3rd or 6th carbon from the terminal methyl group.

This section summarizes the findings of numerous studies from different continents that explored the associations between dietary fatty acids and AMD.

2.1. Polyunsaturated fatty acids (PUFAs)

Omega-3 LC-PUFAs (more than 18 carbon atoms) make up a family of essential fats that human are unable to synthesize *de novo*. Alpha-linolenic acid (ALA) can be converted to the various omega-3 LC-PUFAs including EPA and DHA (Fig. 1). However, these enzymatic conversion efficiencies vary considerably among species and appear to be relatively inefficient in humans (Arterburn et al., 2006). In our ecosystem, algae are the primary producers of EPA and DHA, fish consume algae and therefore are rich in DHA and EPA. Omega-3 LC-PUFAs have important structural and protective functions in the retina (Jeffrey et al., 2001). DHA reaches its highest concentration in the membranes of photoreceptors and is important in photoreceptor differentiation and survival, as well as in retinal function. The anti-inflammatory properties of EPA and DHA (Bazan, 2009; SanGiovanni and Chew, 2005) are of particular interest in AMD, since inflammation appears to have a pivotal role in this condition (Donoso et al., 2006). Finally, omega-3 LC-PUFAs may increase the retinal density of macular pigment, which filters blue light and has local antioxidant and anti-inflammatory activities (Barker et al., 2011; Delyfer et al., 2012; Merle et al., 2017).

2.1.1. Omega-3 PUFAs and fish intake

As displayed in Fig. 2, cross-sectional (Augood et al., 2008; Chong et al., 2009; Delcourt et al., 2007; Heuberger et al., 2001; Mares-Perlman et al., 1995; Parekh et al., 2009; Smith et al., 2000) and case-control studies (Christen et al., 2011; Merle et al., 2014; SanGiovanni et al., 2007; Seddon et al., 2006; Swenor et al., 2010; Zerbib et al., 2014) have shown that subjects affected by AMD tended to have lower intake of fish, the major dietary source of omega-3 fatty acids. Among these studies, five (Augood et al., 2008; Christen et al., 2011; SanGiovanni et al., 2007; Seddon et al., 2006; Swenor et al., 2010) found significant results. Regarding omega-3 LC-PUFAs, subjects with a higher consumption of omega-3 LC-PUFAs were less affected by AMD (Aoki et al., 2016; Augood et al., 2008; Chong et al., 2008; Christen et al., 2011; Merle et al., 2011; SanGiovanni et al., 2007; Seddon et al., 2001, 2006). These associations were significant for all these studies except for two of them (Chong et al., 2008; Seddon et al., 2001).

Cohort studies which assess the risk of developing the disease are a better tool to study the association between dietary fatty acids and AMD. Prospective study designs allow us to rule out the risks of reverse causality, and to confirm the associations between AMD and the consumption of omega-3 PUFAs and fish suggested by cross-sectional and case-control studies. Prospective studies have shown that a high consumption of omega-3 LC-PUFAs (Cho et al., 2001; Chua et al., 2006; Reynolds et al., 2013; SanGiovanni et al., 2008, 2009; Tan et al., 2009; Wu et al., 2017a, 2017b) or fish (Cho et al., 2001; Chua et al., 2006; SanGiovanni et al., 2008; Seddon et al., 2003; Tan et al., 2009) was associated with a reduced risk of developing AMD. For most of them (Cho et al., 2001; Reynolds et al., 2013; SanGiovanni et al., 2008, 2009) these associations were significant. Fig. 3 shows an overview of prospective studies that have been performed in AMD.

In 2008, Chong et al. (2008) performed a meta-analysis, grouping nine previously cited studies: 3 cohort studies (Arnarsson et al., 2006; Cho et al., 2001; Chua et al., 2006), 3 case-control studies (SanGiovanni et al., 2007; Seddon et al., 2001, 2006) and 3 cross-sectional studies (Delcourt et al., 2007; Heuberger et al., 2001; Mares-Perlman et al., 1995). This meta-analysis showed that subjects with high dietary intake of n-3 PUFAs had a 38% decreased risk of AMD (Odds Ratio (OR) = 0.62, 95% Confidence Interval (CI): 0.50–0.80). Regarding fish consumption, subjects with a high intake had a 33% decreased risk of AMD (OR = 0.67, 95% CI 0.53–0.85).

2.1.2. Omega-3 supplementation

To date, two well-conducted randomized, double-blind controlled trials of omega-3 in the prevention of AMD have been conducted.

The Age-Related Eye Disease Study 2 (AREDS2) is a multicenter, randomized phase 3 study involving 4203 participants aged 50–85 years (Age-Related Eye Disease Study 2 Research Group, 2013). Conducted in 2006–2012, this study enrolled participants at risk of progression to advanced AMD with bilateral large drusen or large drusen in one eye and advanced AMD in the fellow eye. The main aim of AREDS2 was to improve the original AREDS formula. In AREDS2, the addition of EPA + DHA to the original AREDS formula did not further reduce the risk of AMD. These results did not support the evidence from laboratory and epidemiological studies, which suggested that omega-3 fatty acids intake have a beneficial effect in the prophylaxis of AMD. One interpretation of these results might be that omega-3 LC-PUFAs supplementation does not protect against AMD progression. However, a deep and detailed analysis of these results lead us to the following conclusion: AREDS2 has not permitted to demonstrate the prophylactic potential role of omega-3 fatty acids and we will give some key points to understand this alternative conclusion.

The nutritional AMD Treatment 2 (NAT-2) study is a randomized, placebo-controlled, parallel, comparative study to evaluate the efficacy of DHA-enriched oral supplementation in preventing neovascularisation (Souied et al., 2013). Two hundred and sixty-three patients, 55–85 years, with early lesions of AMD in the study eye and neovascularisation in the fellow eye were enrolled in 2003–2005. Patients were assigned randomly to receive either an EPA + DHA supplement or the placebo for 3 years. The incidence of neovascularisation was not significantly different between the EPA + DHA group and the placebo group. These results do not appear to differ from AREDS2. However, a subsequent analysis of the NAT-2 data suggested that in the EPA + DHA group, patients steadily achieving the highest tertile of EPA + DHA levels in red-blood cells membranes (RBCM) had significantly lower risk of developing neovascularisation over 3 years.

These two clinical trials are complementary. Despite their similar main result, these studies have an important number of methodological differences (Souied et al., 2015).

Progression to advanced AMD endpoints in the placebo groups of

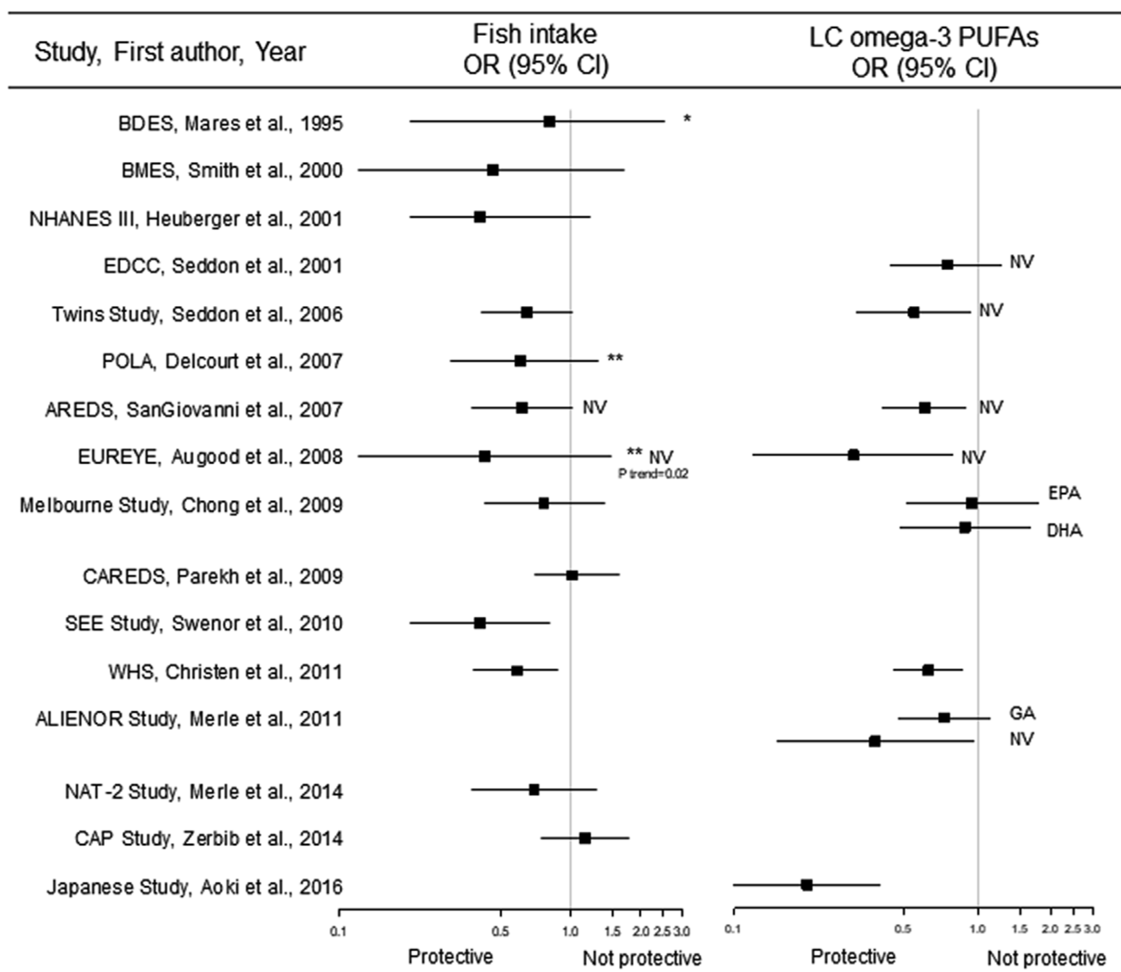


Fig. 2. *Associations between fish intake, dietary long-chain omega-3 polyunsaturated fatty acids and late AMD, cross-sectional and case-controls studies.*
*, Seafood; **, Oily fish; AMD, age-related macular degeneration; CI, confidence interval; GA, geographic atrophy; LC-n-3 PUFA, Long chain n-3 polyunsaturated fatty acid; NV, neovascular disease; OR, odds ratio; BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; NHANES, National Health and Nutrition Examination Survey; EDCC, Eye Disease; POLA, Pathologies Liées à l'Age; AREDS, Age-Related Eye Disease study; EUREYE, European Eye study; CAREDS, Carotenoids Age-Related Eye Disease Study; SEE, Salisbury Eye Evaluation; WHS, Women's Health Study; ALIENOR, Antioxydant LIpides Essentiels Nutrition et maladies OculaiRes; NAT-2, Nutritional AMD Treatment 2; CAP, Créteil AMD PHR-funded.

AREDS was less than expected (Age-Related Eye Disease Study Research Group, 2001). The power calculations in AREDS2 were based on AREDS's expected progression rates. The authors determined the sample size at 90% power to detect a 25% reduction in the progression to advanced AMD, comparing the placebo group with each treatment group (Chew et al., 2012). It is important to keep in mind that 4184 of the 4203 enrolled participants were taking AREDS1 formula, so the 25% effect size would need to exceed the beneficial effect of the AREDS1 formula. This means that if the beneficial effect is lower than 25% it cannot be detect by AREDS2 study design. Omega-3 supplementation might have an effect which could not be detected due to AREDS2 power and effect calculations. A question we should ask ourselves is if the first AREDS study had used omega-3 LC PUFAs alone rather that the current formula and then tested the addition of the current formula to omega-3, whether we would now be using omega-3 LC PUFAs.

In NAT2, the sample size was calculated assuming that the 3-years risk of developing CNV was 19.8% and 33% for the DHA and placebo groups respectively and a power of 80%. In the placebo group, over 3-years CNV incidence was lower than expected (25.6%) and in the supplemented group it was higher than expected (28.4%) which might lead to main results toward null.

It is also important to note that AREDS2 subjects were well eductaed (more than 60% were educated to degree level or higher) and well nourished. Moreover, more than 11.1% of subjects in the control groups took omega-3 LC-PUFAs on their own, contravening to the protocol guidelines, and, these subjects were not further classified by intervention group. This misclassification might lead the main result towards the null (Chew et al., 2014).

Indeed, a number of key baseline nutritional parameters, including serum lutein, zeaxanthin and DHA/EPA, were significantly better in AREDS2 subjects than for the US population, which is unexpected in AMD subjects according to the epidemiological evidence exposed above (Age-Related Eye Disease Study 2 Research Group, 2013; Souied et al., 2015). Results on circulating LC-PUFAs may be used for subgroups analyses as conducted by NAT-2 researchers.

Also, it is important to highlight that the formulations were different with potential differences in bioavailability (AREDS2: ethyl-esters with a DHA/EPA ratio of 1: 2 and NAT-2 triglyceride with a DHA/EPA ratio of 3: 1). AREDS2 and NAT-2 represent important steps forward to understand the roles of micro-nutrition in the prevention of late AMD. More detailed explorations, particularly using different formulations populations and designs, are needed.

2.1.3. Omega-6 PUFAs

Omega-6 PUFAs are known to promote inflammation (De Lorgeril,

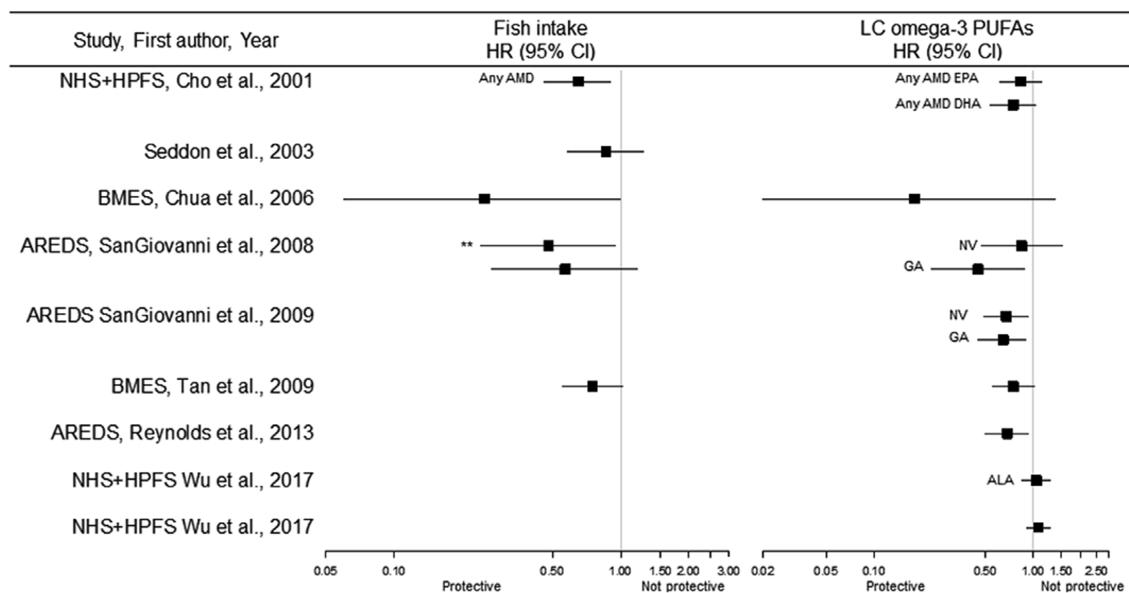


Fig. 3. *Associations between fish intake, dietary long-chain omega-3 polyunsaturated fatty acids and late AMD, prospective studies.*
**, Oily fish; AMD, age-related macular degeneration; CI, confidence interval; GA, geographic atrophy; LC omega-3 PUFA, Long chain n-3 polyunsaturated fatty acid; NV, neovascular disease; HR, Hazard ratio; BMES, Blue Mountains Eye Study; AREDS, Age-Related Eye Disease study; NHS + HPFS, Nurses' Health Study + Health Professional Follow-up Study.

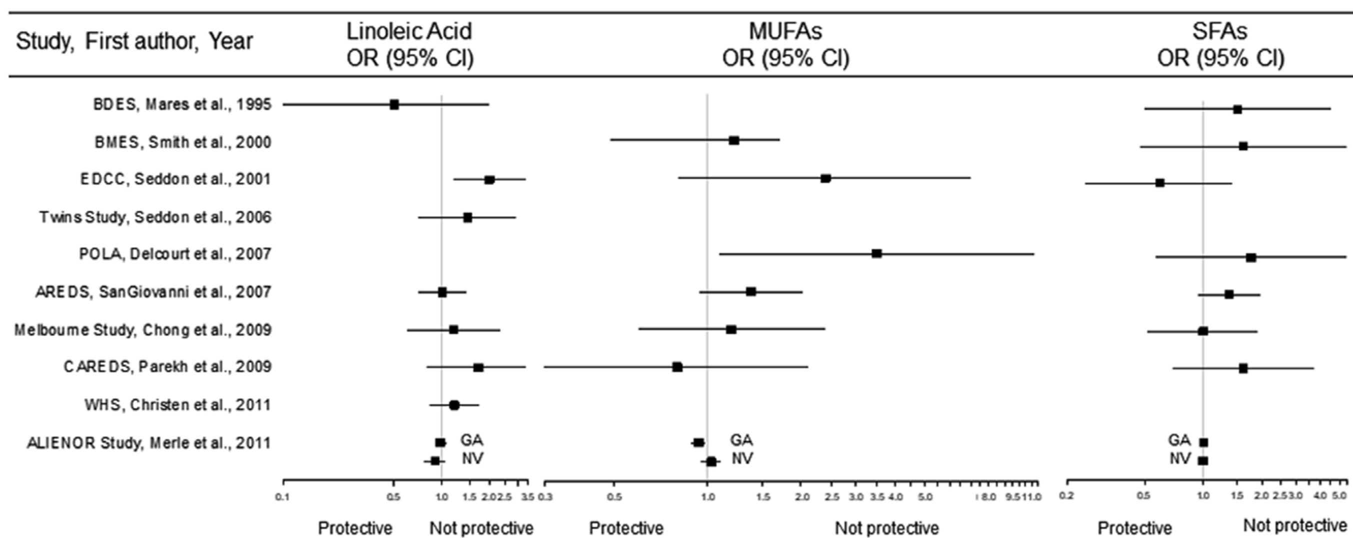


Fig. 4. *Associations between linoleic acid, monounsaturated and saturated fatty acids and advanced AMD, cross-sectional and case-controls studies.*
AMD, age-related macular degeneration; CI, confidence interval; G, geographic atrophy; MUFA, Monounsaturated fatty acid; NV, neovascular disease; OR, odds ratio; SFA, saturated fatty acid; BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; EDCC, Eye Disease; POLA, Pathologies Liées à l'Age; AREDS, Age-Related Eye Disease study; CAREDS, Carotenoids Age-Related Eye Disease Study; WHS, Women's Health Study; ALIENOR, Antioxydant LIpides Essentiels Nutrition et maladies OculaiRes.

2007), which is thought to contribute to retinal damage that may initiate AMD (Anderson et al., 2002). Epidemiological studies have reported that a high intake of omega-6 PUFAs or the major omega −6 PUFA (linoleic acid) tended to be associated with a higher risk of AMD (Cho et al., 2001; Chong et al., 2009; Christen et al., 2011; Chua et al., 2006; Mares-Perlman et al., 1995; Merle et al., 2011; Parekh et al., 2009; Reynolds et al., 2013; SanGiovanni et al., 2007; Seddon et al., 2001, 2006; Tan et al., 2009) but very few studies reported significant associations (Seddon et al., 2001) (Figs. 4 and 5).

2.2. Monounsaturated fatty acids (MUFAs)

Associations between MUFAs and AMD are not consistent across epidemiological studies (Cho et al., 2001; Chong et al., 2009; Chua et al., 2006; Delcourt et al., 2007; Merle et al., 2011; Parekh et al., 2009; Reynolds et al., 2013; SanGiovanni et al., 2007; Seddon et al., 2001, 2003; Smith et al., 2000; Tan et al., 2009) and very few showed significant results (Figs. 4 and 5). Those results are not convincing for a potential role of MUFAs in the prevention of AMD.

Among MUFAs, oleic acid might have a protective effect on AMD, but very few studies have assessed association between oleic acid and AMD. Olive oil consumption, which is one of the main sources of oleic acid in our diet, has been significantly associated with a lower risk for AMD in Australian (Chong et al., 2009) and French (Cougnard-Gregoire et al., 2016) studies. Moreover, olive oil also contains other components such as polyphenols, which might have a protective role in AMD, thus it

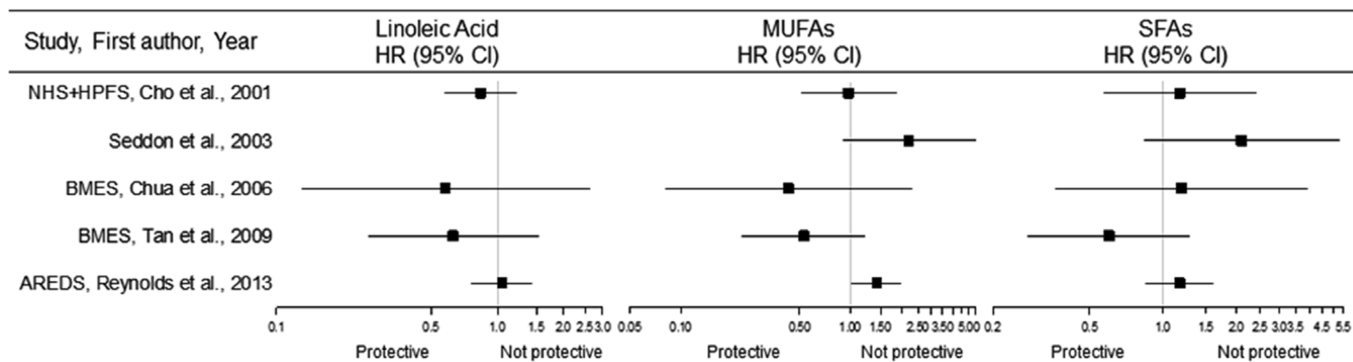


Fig. 5. *Associations between linoleic acid, monounsaturated and saturated fatty acids and advanced AMD, prospectives studies.*
AMD, age-related macular degeneration; CI, confidence interval; GA, geographic atrophy; MUFA, monounsaturated fatty acid; NV, neovascular disease; HR, Hazard ratio; SFA, saturated fatty acid; BMES, Blue Mountains Eye Study; AREDS, Age-Related Eye Disease study; NHS + HPFS, Nurses' Health Study + Health Professional Follow-up Study.

is difficult to differentiate whether the health benefits are attributable to oleic acid or other components of olive oil.

2.3. Saturated fatty acids (SFAs), trans-SFAs and dietary cholesterol

Most epidemiological studies suggested that a high consumptions of SFA (Cho et al., 2001; Chong et al., 2009; Chua et al., 2006; Delcourt et al., 2007; Mares-Perlman et al., 1995; Merle et al., 2011; Parekh et al., 2009; Reynolds et al., 2013; SanGiovanni et al., 2007; Seddon et al., 2001, 2003; Smith et al., 2000; Tan et al., 2009) or trans-SFAs (Cho et al., 2001; Chong et al., 2009; Chua et al., 2006; Parekh et al., 2009; Seddon et al., 2003) were associated with an increased risk of AMD, but most of the results were not statistically significant (Figs. 4 and 5). Epidemiological studies do not allow us to conclude that high consumption of SFAs and trans-SFAs are a risk factor for AMD. Dietary cholesterol was not associated with AMD (Cho et al., 2001; Mares-Perlman et al., 1995; SanGiovanni et al., 2007; Seddon et al., 2001) except in one study showing that a higher dietary intake of cholesterol was associated with a higher risk of developing AMD (Smith et al., 2000).

2.4. Biomarkers of dietary lipid intake in AMD

Dietary assessment methods rely on the subjects' memory and perceptions, and face the difficulties of extreme day-to-day variability of the human diet, the hidden nature of many fats used for dressing and cooking, the bias in reporting due to social standards and nutritional recommendations, and the estimation of the nutritional content of foods. Because of the multiple difficulties of dietary assessment, circulating biomarkers may represent a more objective alternative for the assessment of nutritional status. The Alienor (Merle et al., 2013a) and the NAT-2 (Merle et al., 2014) studies explored the associations between EPA and DHA measured in plasma and RBCM and the risk of late AMD. The Alienor study reports that high plasma total omega-3 PUFAs was significantly associated with a 38% reduction of the odds of late AMD ($n = 605$ subjects, OR for 1-SD increase: 0.62 95% CI 0.44–0.88 $p = 0.008$) and these results were confirmed by the NAT-2 study (DHA: OR Tertile 3 (> 0.9% of the total fatty acids) vs. Tertile 1(< 0.5%): 0.41 95% CI 0.22–0.77 p for trend = 0.005). Moreover, the NAT2 study showed that a high RBCM EPA + DHA index, a longer-term biomarker of dietary omega-3 PUFAs, was significantly associated with a reduced risk of neovascularisation (OR Tertile 3 (> 4.6%) vs. Tertile 1(< 3.5%): 0.52 95% CI 0.29–0.94 p for trend = 0.03).

These biomarkers are of utmost interest to help identify high-risk subjects, who may benefit most from nutritional intervention. Such biomarkers also might be used to follow the efficacy of nutritional interventions in restoring adequate nutritional status.

3. Circulating lipoproteins and AMD

Lipids, such as cholesterol and triglycerides (TG), have many important functions in the human body. They play a role in energy storage, cell signaling and are a fundamental component of cell membranes. However, cholesterol and triglycerides are insoluble in water (Fahy et al., 2005). They dependent on transport vehicles, called lipoproteins, for transportation through the circulation (Hegele, 2009). Lipoproteins is a group of particles with different biochemical composition as well as physico-chemical and biological properties. Lipoproteins are commonly classified in 5 classes according to their density (Fig. 6). These classes have been intensively investigated for their role in physiology and clinical diagnosis.

Dyslipidemia, the altered levels of circulating cholesterol, TG or

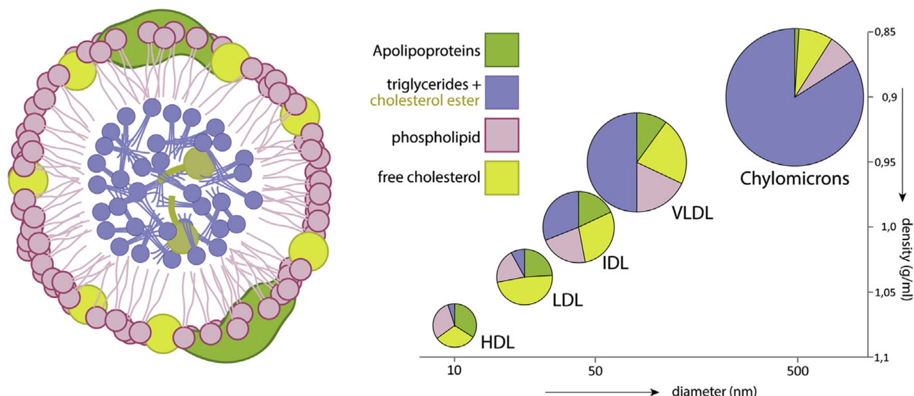


Fig. 6. *Composition and main physical-chemical properties of major lipoproteins classes.*
Left; The outer shell of lipoproteins consists of a phospholipid and cholesterol, combined with apolipoproteins, which defines that type, function and/or destination of the lipoprotein. Hydrophobic lipids (triglycerides, cholesterol esters) are in the core of the lipoprotein. Right; Lipoproteins are classified according to their size, density and composition. HDL, high-density lipoprotein; LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; VLDL, very low-density lipoprotein.

lipoproteins, is indisputably associated with cardiovascular disease (CVD), and for decades measurement of circulating lipoproteins levels (i.e. total cholesterol, LDL-C and HDL-C) has been part of routine clinical practice for risk prediction and monitoring treatment effects in CVD (Piepoli et al., 2016). As lipoproteins metabolism also appears to play an important role in AMD (Snow and Seddon, 1999), in this section, we review the numerous studies that evaluated the association between circulating lipid levels and development of AMD (Kersten et al., 2018).

3.1. Associations between circulating lipoproteins and AMD

The most frequently studied lipoprotein measurement in AMD is total cholesterol (TC), which is a measure of the total amount of cholesterol contained in all circulating lipoproteins. The majority of studies reported no or only a weak association between TC and AMD (Kersten et al., 2018). A recent meta-analysis including 18 studies, however, showed a protective tendency for increased levels of TC and AMD, but this association was only significant in early AMD (Hegele, 2009; Wang et al., 2016b).

TG represent the main constituent of body fat and are an important source of energy (Hegele, 2009; Sarwar et al., 2007). Although most studies did not demonstrate an association between TG and AMD, several studies reported lower TG levels in AMD compared to control individuals (Kersten et al., 2018). Additionally, meta-analysis of 9 studies evaluating TG levels in AMD demonstrated that an increase in TG levels was associated with a decreased risk of early, but not late, AMD (Wang et al., 2016b). These results indicate a potential inverse relationship between TG and AMD, and surprisingly is opposite to the positive association of TG and CVD (Sarwar et al., 2007).

Other circulating lipoprotein measurements that have recurrently been reported in AMD include low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). LDL-C is the main carrier of cholesterol in the circulation. While a number of small case-control studies described increased LDL-C levels in AMD, most population-based studies did not report significantly different LDL-C levels between AMD patients and controls (Kersten et al., 2018). Moreover, increased LDL-C tended to have a protective effect in a meta-analysis of several larger studies (Wang et al., 2016b). This contrasts the association between LDL-C and CVD, where increased LDL-C levels are associated with the disease due to its atherogenic properties (Cholesterol Treatment Trialists et al., 2010; Piepoli et al., 2016). It must be noted that the majority of studies did not directly measure LDL-C, but calculated its levels using the Friedewald's formula. This formula, based on several assumptions, has limitations and therefore direct measurement of LDL-C is recommended (European Association for Cardiovascular et al., 2011).

Lipoprotein(a) (Lp(a)) is a lipoprotein that is highly associated with CVD (Waldeyer et al., 2017). In early and neovascular AMD, Lp(a) levels had been shown to be significantly increased in the choroidal arteries (Bhutto and Lutty, 2012), therefore, Lp(a) may represent a possible risk factor of AMD. Although at plasma level, it was shown to be statistically significant different between AMD patients and control for CRP and not for Lp(a) (Chirco and Potempa, 2018; Colak et al., 2011; Mitta et al., 2013), due to its association with CRP (McLaughlin et al., 2002; Rallidis et al., 2002), it is suggested that Lp(a) is involved in the local inflammation and cellular injury in the RPE/choroid.

Epidemiological studies evaluating circulating HDL-C levels in AMD also show mixed results. In a recent review of 55 studies that measured HDL-C levels in AMD, the majority (34 studies) showed no association, 16 studies showed higher HDL-C levels in AMD, and 5 studies showed lower HDL-C levels in AMD compared to controls (Kersten et al., 2018). However, it should be noted that studies often lack association due to relatively small sample sizes. Results of a meta-analysis covering 15 studies suggest an increased risk of AMD in subjects with high HDL-C, although this was not significant (Wang et al., 2016b). Recent Mendelian randomization studies using genetic variants associated with lipid fractions support the hypothesis that elevated HDL-C is associated with an increased AMD risk, see also section 4.4 (Burgess and Davey Smith, 2017).

In conclusion, conflicting associations between circulating lipoproteins levels and AMD have been described, but there is growing evidence that increased HDL-C levels might be associated with higher risk for AMD. However, assessing HDL functionality rather than measuring systemic levels might provide additional insights in AMD pathogenesis (Cougnard-Gregoire et al., 2014; Wang et al., 2016b).

3.2. Function and composition of HDL

In conditions characterized by inflammation and oxidative stress HDL can convert into dysfunctional particles that can promote inflammation and LDL oxidation (Eren et al., 2012; G et al., 2011). HDL is a set of particles with a heterogeneous biochemical composition as well as distinct physicochemical and biological properties that can change in several diseases, pathological conditions, through diet and lifestyle changes and can also be altered by genetic variations (Asztalos and Schaefer, 2003; Connelly et al., 2016; Kontush et al., 2015; Rosenson et al., 2011, 2013, 2016; Rye and Barter, 2014). Changes in HDL composition and functionality might be better associated with AMD than total circulating plasma levels.

There is only one study published so far on the composition and biological properties of HDL particles in AMD (Pertl et al., 2016). The authors found that serum amyloid A was significantly increased in AMD patients after adjusting for age, gender, body mass index (BMI), C-reactive protein (CRP) level and other covariates. However, the concentration of apolipoprotein A-I (APOA1), A-II (APOA2), apolipoprotein C-III, apolipoprotein E (APOE), TC, non-esterified cholesterol, TG, phospholipids and fatty acids of HDL did not differ between AMD and control groups. The authors also analyzed HDL biological activities and reported differences in cholesterol efflux and anti-oxidative activity (measured by dihydrorhodamine oxidation and PON1 activity assays), anti-inflammatory activity (inhibition of lipopolysaccharide-induced activation of NF-kB in monocytes) and lipoprotein-associated phospholipase A2 activity in AMD patients compared to controls.

Work on the complement system in AMD pathogenesis has received significant attention and that work in recent years has been translated to explorations on the use of complement inhibitors in human clinical trials on AMD (Geerlings et al., 2017; Williams et al., 2014; Xu and Chen, 2016). There are several classes of lipoprotein particles and a number of these are linked functionally and/or structurally to the complement system. The largest and least dense are chylomicron particles that are involved in carrying lipids from the intestine to the rest of the body. Chylomicrons also carry transthyretin which has been shown to stimulate Complement C3 (C3) and acylation stimulating protein (C3desArg) synthesis (Scantlebury et al., 1998) in a dose dependent manner, offering evidence for an intricate connection between complement components and lipid homeostasis. On the other end of the density spectrum is the HDL. APOA1 and APOA2 that are contained within it, were shown to inhibit complement-mediated lysis (Rosenfeld et al., 1983). Another component of HDL is apolipoprotein J (ApoJ, also known as clusterin) that was suggested to be a central player in the inhibition of complement-mediated lysis (Jenne et al., 1991) via binding to complement C7, complement C8 and complement C9 (C9) (Tschopp et al., 1993). APOE, another HDL component, binds to complement factor H (CFH) (via domains 5–7), thereby regulating complement activation (Haapasalo et al., 2015). Therefore, HDL can be directly involved in complement regulation and AMD.

Links between lipoproteins and the complement system deepened once it was evidenced that clusterin was not the only complement-related protein to be carried by the HDL particle. In a proteomic study of HDL, several complement components were identified such as C3, complement factor C4B, Factor B, complement C5 and to a lesser extent

Table 1
Variants in or near genes encoding components of the lipid metabolism, reported to be associated with AMD at genome wide level ($p < 5 \times 10^{-8}$) (Fritsche et al., 2016).

Gene	Variant	Position in gene	Minor allele	Minor allele frequency		Association results	
				Cases	Controls	OR	P
ABCA1	rs2740488	intronic	C	0.255	0.275	0.89	6.0×10^{-7}
LIPC	rs2043085	21 kb upstream	C	0.350	0.381	1.15	7.7×10^{-13}
LIPC	rs2070895	intronic	A	0.195	0.217	0.86	1.8×10^{-10}
CETP	rs5817082	intronic	CA	0.232	0.264	0.87	2.7×10^{-8}
CETP	rs17231506	1 kb upstream	T	0.348	0.315	1.11	1.2×10^{-6}
APOE	rs429358	coding; Cys156Arg	C	0.099	0.135	0.67	3.9×10^{-39}
APOE (EXOC3L2/MARK4)	rs73036519	distant; 335 kb downstream	C	0.284	0.302	0.91	2.4×10^{-5}

complement C1 subcomponents and complement C2 (Gordon et al., 2010). Similar to HDL Lp(a) were also associated with 35 proteins among which are components of the complement system (von Zychlinski et al., 2011). There is evidence that subsets of HDL carry very specific complement components or regulators. In one lipoprotein fraction complement factor H-related (CFHR) proteins were discovered and this study observed that all of the CFHR1 in plasma located to this lipoprotein fraction (Park and Wright, 1996). Later, dimerized forms of CFHR4 (Skerka et al., 1997) and CFHR5 (McRae et al., 2005) were found to be associated with triglyceride-rich lipoproteins. This lipoprotein fraction was identified to be a small subfraction of HDL (about 2% of APOA1 containing HDL, with high density) that was named Factor H-related protein associated lipoprotein particle (Park and Wright, 1996, 2000). Although the precise function of the presence of complement components and regulators in the lipoprotein fractions remains unknown, the intimate link between the two systems becomes ever more apparent.

Further complexities are highlighted in observations suggesting that the protein content of the HDL particle is not static, but dynamic. For example, in coronary artery disease (CAD) C3 and complement C4 were elevated in the HDL fraction compared to controls while clusterin was reduced, suggesting that under specific conditions the inflammatory profile of HDL particle can change (Vaisar et al., 2007). Under the influence of statins and niacin, the composition of HDL could be remodeled to resemble HDL normally found in healthy subjects (Green et al., 2008). This observation is not limited to coronary artery disease. In rheumatoid arthritis, changes in HDL composition were also reported (factor B, C3 and C9 were increased in this condition) (Watanabe et al., 2012).

Taken together, these studies suggest that circulating lipoproteins levels and both composition and biological activity of HDL might be important in the pathogenesis of AMD.

4. Genetic associations of variants in lipoprotein metabolism genes in AMD

The evidence for a genetic contribution to the development of AMD comes from epidemiological twin studies (Hammond et al., 2002; Klein et al., 1994, 2001a; Meyers et al., 1995; Seddon et al., 1997), family-based linkage studies (Klein et al., 1998; Schultz et al., 2003; Seddon et al., 1997), candidate gene studies (Helgason et al., 2013; Klaver et al., 1998; Raychaudhuri et al., 2011; Seddon et al., 2013; Zhan et al., 2013) and GWAS (Chen et al., 2010; Fritsche et al., 2013, 2016; Neale et al., 2010; Yu et al., 2011a). This section focuses on the genes involved in AMD and in subtypes of AMD. Next, we discuss the genetic overlap between circulating lipids and AMD.

4.1. Genes involved in AMD

The most recent GWAS in AMD analyzed 16,144 patients with late AMD and 17,832 controls of European ancestry using exome arrays (Fritsche et al., 2016). This genome-wide analysis of > 12 million genotyped or imputed variants resulted in 52 independent variants with genome-wide significant association (*p*-value ≤ 5E-8). These variants are distributed across 34 genomic regions, of which 18 loci were already known by previous GWAS (Fritsche et al., 2013; Seddon et al., 2013). In total, the 52 identified variants explain more than half of the genomic heritability of AMD. In addition, a gene-based test for the cumulative effect of rare variants revealed a burden of rare variants in 4 genes: *CFH*, Factor I (*CFI*), tissue inhibitor of metalloproteinase 3 *(TIMP3)* and solute carrier family 16 member 8 genes (Fritsche et al., 2016). Recent candidate gene studies also revealed rare variants within the *CFH*, *CFI*, *C3* and *C9* genes, some with large effect sizes, explaining a small fraction of the heritability of AMD (Helgason et al., 2013; Raychaudhuri et al., 2011; Seddon et al., 2013; van de Ven et al., 2013; Zhan et al., 2013). Additional rare variants may be identified using exome and whole genome sequencing in large AMD case-control cohorts (den Hollander and de Jong, 2014).

Although the exact role of the identified variants in AMD pathogenesis remains to be elucidated, the expression and function of the genes at the AMD-associated loci can shed light on the disease etiology. 82.6% of the genes within the genomic regions discovered to be associated with AMD by Fritsche et al. (2016) are expressed in the retina and 86.4% of these genes are expressed in, but not specific for, the RPE/choroid, supporting a role for these genes at the disease site. Consulting the gene ontology database showed that several of the genes within AMD loci are involved in the complement system, lipid metabolism and extracellular matrix remodeling (Fritsche et al., 2016).

AMD-associated genetic variants in the lipid metabolism were identified in or near the ATP binding cassette subfamily A member 1 (*ABCA1*), *APOE*, cholesteryl ester transfer protein (*CETP*) and hepatic lipase C (*LIPC*) genes (Table 1) (Fritsche et al., 2016). One intronic variant (rs2740488) in the *ABCA1* gene is protective for AMD, with a modest effect size (OR 0.89). Two variants in or near the *LIPC* gene are independently associated with AMD. The first variant (rs2043085) is located 21 kb upstream of the *LIPC* gene and is associated with an increased risk for AMD, however, with a modest effect size (OR 1.15). A second intronic variant (rs2070895) is slightly protective for AMD (OR 0.86). Two variants in or near the *CETP* gene are independently associated with AMD. The first intronic variant (rs5817082) is slightly protective for AMD (OR 0.87), while the second variant (rs17231506) located 1 kb upstream of the *CETP* gene gives a slight risk for AMD (OR 1.11). A coding variant (rs429358) in the *APOE* gene, which defines the APOEe4 allele, introduces an amino acid change (c.466C > T; p.Cys156Arg) and is protective for AMD (OR 0.67). A variant (rs73036519) located at 335 kb distance of the *APOE* gene (between the *EXOC3L2* and *MARK4* genes) is slightly protective for AMD (OR 0.91). The effect of these variants on gene regulation, gene expression, and protein function is currently unknown, with the exception of rs429358 (APOE e4 allele), a coding nonsynonymous variant (p.Cys156Arg) which alters the lipoprotein binding properties of APOE (Weisgraber, 1990). Although these variants represent the top AMD-associated signals at these loci, they

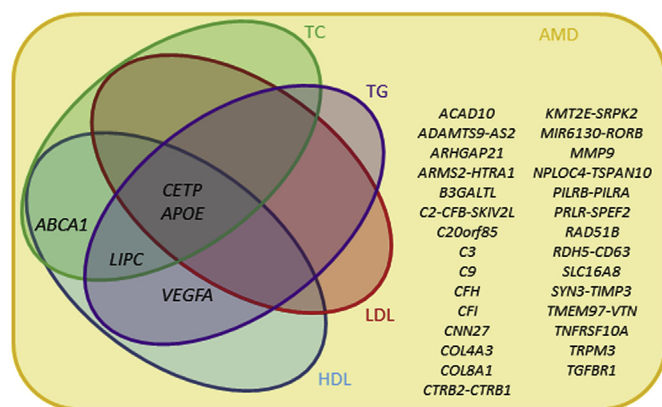


Fig. 7. *The overlap between genes identified by GWAS of blood lipid levels and the genes identified by GWAS of AMD.*
Five of the genes identified by the largest GWAS to be associated with AMD (Fritsche et al., 2016) are also associated by GWAS with blood lipid levels. Only loci that overlap between the variants found for AMD and the variant found blood lipid levels are considered overlapping loci. GWAS, genome-wide association study; AMD, age-related macular degeneration.

may not represent the causative variant involved in the disease. Due to the genomic haploblock structure, any other variant in high linkage disequilibrium with the top AMD-associated signal may be the causative variant. Further research is needed to understand the effects of each of these variants on the disease mechanisms. So far, no rare variants with large effect sizes have been identified in genes of the lipid metabolism in AMD.

So far, no rare variants with large effect sizes have been identified in genes of the lipid metabolism in AMD.

4.2. Genetic background of subtypes of AMD

AMD patients can be divided into several subgroups, including early AMD, neovascularisation and GA (Ferris et al., 2013; Klein et al., 2014a). Several studies have evaluated the genetic background of these AMD subtypes, as this may identify targets for therapeutic intervention in these AMD subgroups. It should be kept in mind that the sample sizes of these studies are generally small, and it is known that study size is a crucial determinant of the power to detect a disease-associated variant (Spencer et al., 2009).

A study by Sobrin et al. (2012) compared the two late AMD subtypes, neovascularisation and GA. The *ARMS2-HTRA1* (age-related maculopathy susceptibility 2 - high-temperature requirement A Serine Peptidase 1) locus showed a significant difference between disease subtypes. This finding was confirmed by Fritsche et al. (2016), who also compared neovascularisation and GA. That study also identified a significant difference between disease subtypes for genetic variants at the *CETP* and *SYN-TIMP3* (Synapsin-TIMP3) loci. Furthermore, they showed that a variant close to the matrix metallopeptidase 9 (*MMP9*) gene was exclusively associated with neovascularisation but not with GA. This is in line with the previous evidence that upregulation of *MMP9* appears to induce neovascularisation (Lambert et al., 2014) and interacts with VEGF signaling in the RPE (Hollborn et al., 2007).

A comparison between intermediate AMD and late AMD showed that seven extracellular matrix genes are associated only with late AMD (Fritsche et al., 2016), which may lead to the hypothesis that extracellular matrix variation represents a disease subtype with extremely rapid progression. This hypothesis is still to be confirmed though.

4.3. Genetic overlap between AMD and circulating lipoprotein levels

Over the last decade many variants have been identified to be associated with HDL-C, LDL-C, TC and TG levels. In 2010 Teslovich et al. published the first large GWAS on circulating lipid and lipoprotein levels of > 100,000 individuals imputed with the HapMap reference panel (International HapMap, 2005; International HapMap 3 Consortium et al., 2010; International HapMap Consortium et al., 2007). They reported 95 significantly associated loci which in total explain 25–30% of the genetic variance for each trait (Teslovich et al., 2010). By increasing the sample size to 188,577 individuals, 62 additional loci have been identified to be associated with circulating lipid levels in humans (Willer et al., 2013). The availability of improved reference panels, both in the number of variants as in the number of individuals, like the 1000 Genomes reference panel (Genomes Project et al., 2010, 2012) and the Genome of the Netherlands (Boomsma et al., 2014; Genome of the Netherlands, 2014) reference panel, resulted in the identification of 22 additional loci (Surakka et al., 2015; van Leeuwen et al., 2015b, 2016) for circulating lipid levels and fine-mapping of the known loci (van Leeuwen et al., 2015a). Many of the identified loci associated with circulating lipid levels are also associated with cardiovascular and metabolic traits, including coronary artery disease, type 2 diabetes, blood pressure, waist-hip ratio and body mass index (Willer et al., 2013). So far, GWAS have identified common and low-frequency variants. The last few years, with the newest techniques available like whole-exome sequencing and the exome chip, also rare variants with larger effects on circulating lipid and lipoprotein levels have been identified (Lange et al., 2014; Peloso et al., 2014), however these rare variants are mainly within loci already identified to be associated with circulating lipid and lipoprotein levels.

The loci identified by the various GWAS show that there is a large overlap between the genetic background of HDL-C, LDL-C, TC and TG levels. Some of the loci have also been identified by GWAS to be associated with AMD (Fritsche et al., 2016) (Fig. 7). Of all 52 loci associated with AMD, the *ABCA1, APOE, CETP, LIPC* and vascular endothelial growth factor A (*VEGFA*) loci are associated also with HDL-C, LDL-C, TC and/or TG levels. Of these genes, *ABCA1, APOE, CETP* and *LIPC* encode proteins involved in cholesterol transport, while *VEGFA* belongs to the group of genes which promote angiogenesis.

One of the first reported genetic associations with AMD was the protective effect exerted by the ε4 haplotype of the *APOE* gene, encoding a lipid transport protein that acts as a ligand for the LDL-C receptor, which is involved in the maintenance and repair of neuronal cell membranes (Klaver et al., 1998; Souied et al., 1998). The protein encoded by the *APOE* gene is a major transporter of lipids and cholesterol in the central nervous system (Tai et al., 2016). This protein is also expressed in the retina where it plays a role in local trafficking of lipids (section 5.2) and besides exerting a protective effect for AMD, it also acts as a risk factor for Alzheimer's disease (Soffientini and Graham, 2016). Teslovich et al. reported rs4420638, an intergenic variant near the *APOE* gene to be associated with HDL-C ($\beta = -1.06$ for the minor G allele, *p-value* 4.40×10^{-21}), LDL-C ($\beta = 7.14$ for the minor G allele, *p-value* 8.72×10^{-147}) and TC ($\beta = 6.83$ for the minor G allele, *p-value* 5.20×10^{-111}) (Teslovich et al., 2010). The rs4420638 variant is in linkage disequilibrium ($r^2 = 0.72$) with the AMD-associated variant rs429358 identified by Fritsche et al. (Table 2) (Fritsche et al., 2016). The HDL-C-lowering, LDL-C-elevating and TC-elevating minor G allele of rs4420638 is co-inherited with the AMD-protective minor C allele of rs429358. Teslovich et al. also reported rs439401, another intergenic variant near the *APOE* gene to be associated with TG ($\beta = -5.50$ for the T allele, *p-value* 1.1×10^{-30}) (Teslovich et al., 2010).

LIPC encodes hepatic triglyceride lipase, which is expressed in liver. LIPC has the dual functions of triglyceride hydrolase and ligand/bridging factor for receptor-mediated lipoprotein uptake. Teslovich et al. reported rs1532085, an intergenic variant near the *LIPC* gene to be associated with HDL-C ($\beta = 1.45$ for the minor A allele, *p-value* 2.92×10^{-96}) and TC ($\beta = 1.54$ for the minor A allele, *p-value* $= 8.83 \times 10^{-20}$) (Teslovich et al., 2010). The rs1532085 variant is in high linkage disequilibrium ($r^2 = 0.96$) with the AMD-associated variant rs2043085 identified by Fritsche et al. (Table 2) (Fritsche et al.,

Table 2
Variants in or near genes encoding components of the lipid metabolism, reported to be associated with lipid or lipoprotein levels.

Gene	Variant	Minor allele	Effect on lipid or lipoprotein level (Willer et al., 2013; Teslovich et al., 2010)			Linkage disequilibrium with AMD SNP (Fritsche et al., 2016) (r^2)[a]
			Lipid/lipoprotein	β for minor allele	p-value	
APOE	rs4420638	G	HDL-C	−1.06	4.40×10^{-21}	0.72 with rs429358
			LDL-C	7.14	8.72×10^{-147}	0.02 with rs73036519
			TC	6.83	5.20×10^{-111}	
APOE	rs439401	T	TG	−5.50	1.14×10^{-30}	0.12 with rs429358
						0.0001 with rs73036519
LIPC	rs1532085	A	HDL-C	1.45	2.92×10^{-96}	0.96 with rs2043085
			TC	1.54	8.83×10^{-20}	0.002 with rs2070895
LIPC	rs261342	G	TG	2.99	2.42×10^{-13}	0.0016 with rs2043085
						0.88 with rs2070895
CETP	rs3764261	A	HDL-C	3.39	7.10×10^{-380}	0.18 with rs5817082
			TC	1.67	6.67×10^{-14}	1.0 with rs17231506
CETP	rs247616	T	LDL	−1.45	9.25×10^{-13}	0.18 with rs5817082
						1.0 with rs17231506
CETP	rs7205804	A	TG	−2.88	1.15×10^{-12}	0.31 with rs5817082
						0.52 with rs17231506
ABCA1	rs1883025	T	HDL-C	−0.94	1.75×10^{-33}	0.94 with rs2740488
			TC	−2.24	3.39×10^{-27}	
VEGFA	rs998584	A	HDL-C	−0.026	2×10^{-11}	0.0002 with rs943080
			TG	0.029	3×10^{-15}	

[a] r^2 was calculated for the European population (CEU) using LDpair in the LDlink web-application (https://analysistools.nci.nih.gov/LDlink/).

2016). The HDL-C-elevating and TC-elevating minor A allele of rs1532085 is co-inherited with the AMD-protective T allele of rs2043085. Teslovich et *al* also reported rs261342, another intergenic variant near the *LIPC* gene to be associated with TG (β = 2.99 for the minor G allele, *p-value* 2.42×10^{-13}) (Teslovich et al., 2010). The rs261342 variant is in linkage disequilibrium ($r^2 = 0.88$) with the AMD-associated variant rs2070895 identified by Fritsche et al. (Table 2) (Fritsche et al., 2016). The TG-elevating minor G allele of rs261342 is co-inherited with the AMD-protective minor A allele of rs2070895.

The protein encoded by the *CETP* gene is the key participant in the reverse transport of cholesterol from the artery walls to the liver (Zhong et al., 1996), as shown by functional analyses in mice (Hayek et al., 1995), hamsters (Briand et al., 2014) and rabbits (Kee et al., 2006). Expression of *CETP* was also detected in the neural retinal and RPE, and the protein was found to localize to the interphotoreceptor matrix (Tserentsoodol et al., 2006a; Zheng et al., 2012), where it is involved in local lipid trafficking (section 5.2). Three variants in or near the *CETP* gene have shown to be associated with lipoprotein levels (Teslovich et al., 2010). The intergenic variant rs3764261 located upstream of the *CETP* gene is associated with TC (β = 1.67 for the minor A allele, p-value 6.67×10^{-14}) and with HDL-C (β = 3.39 for the minor A allele, p-value 7.10×10^{-380}). Another intergenic variant, rs247616, is associated with LDL-C (β = −1.45 for the minor T allele, p-value 9.25×10^{-13}). The intronic variant rs7205804 is associated with TG (β = −2.88 for the minor A allele, p-value 1.15×10^{-12}). The rs3764261 and rs247616 are in high linkage disequilibrium ($r^2 = 1.0$) with the AMD-associated variant rs17231506 identified by Fritsche et al. (Table 2). The HDL-C-elevating and TC-elevating minor A allele of rs3764261 and the LDL-C-lowering minor T allele of rs247616 are co-inherited with the AMD-risk minor T allele of rs17231506.

The *ABCA1* gene encodes a membrane-associated protein, which functions as a cholesterol efflux pump in the cellular lipid removal pathway (Huang and Zhang, 2013) and therefore plays a protective role in the HDL-C pathway. A recent study demonstrated that ABCA1 is expressed in the RPE, where it plays a role in cholesterol efflux from the RPE (Storti et al., 2017) (section 5.2). A meta-analysis of 12 studies (Chen et al., 2010; Dietzel et al., 2014; Fauser et al., 2011; Li et al., 2014; Merle et al., 2013b; Neale et al., 2010; Peter et al., 2011; Sobrin et al., 2012; Wang et al., 2015; Yu et al., 2011a, 2011b; Zhang et al., 2013) which assessed the association between the *ABCA*1 rs1883025 polymorphism and AMD, showed significant association with the lower risk of overall AMD (*OR* = 0.81). The same SNP (rs1883025) was also reported by Teslovich et al. to be associated with HDL-C (β = −0.94 for the minor T allele, *p-value* 1.75×10^{-33}) and TC (β = −2.24 for the minor T allele, *p-value* 3.39×10^{-27}) (Teslovich et al., 2010). The rs1883025 variant is in high linkage disequilibrium ($r^2 = 0.94$) with the top AMD-associated SNP rs2740488 in the GWAS by Fritsche et al. (2016). The HDL-C-lowering and TC-lowering minor T allele of rs1883025 is co-inherited with the AMD-protective minor C allele of rs2740488.

VEGF is a key molecule in promoting angiogenesis and potentially inducing vascular leakage and inflammation by triggering the increased production and permeability of capillary endothelial cells (Ferrara et al., 2003). The VEGF family comprises of several members, among which VEGFA, which plays a role in the pathophysiology of neovascularisation. High concentrations of VEGFA and its receptors are found in the membranes of surrounding tissues and RPE cells (Kliffen et al., 1997; Kvanta et al., 1996; Tatar et al., 2006). In 2013, Huang et al. (2013) meta-analyzed all studies published so far (Almeida et al., 2012; Churchill et al., 2006; Francis et al., 2009; Galan et al., 2010; Immonen et al., 2010; Janik-Papis et al., 2009; Lin et al., 2008; Qu et al., 2011; Richardson et al., 2007) in which the association between AMD and *VEGFA* polymorphisms (rs1413711, rs833061, rs2010963 and rs3025039) was tested. The top AMD-associated variant identified in the GWAS by Fritsche et al. is rs943080, which exerts a protective effect for AMD (OR 0.87) (Fritsche et al., 2016). The Global Lipids Genetics consortium reported rs998584, an intergenic variant near the *VEGFA* gene to be associated with HDL-C (β = −0.026 for the minor A allele and *p-value* = 2×10^{-11}) and TG (β = 0.029 for the minor A allele and *p-value* = 3×10^{-15}) (Willer et al., 2013). The rs998584 variant is not in linkage disequlibrium with the AMD-associated variant rs943080 (Table 2).

4.4. Mendelian randomization

Two reports investigating the causal role of plasma lipoproteins in AMD using Mendelian randomization methods have been recently published (Burgess and Davey Smith, 2017; Fan et al., 2017). Mendelian randomization is a relatively new approach that uses genetic variants associated with a modifiable exposure or biological intermediate to estimate the causal relationship between these variables and a

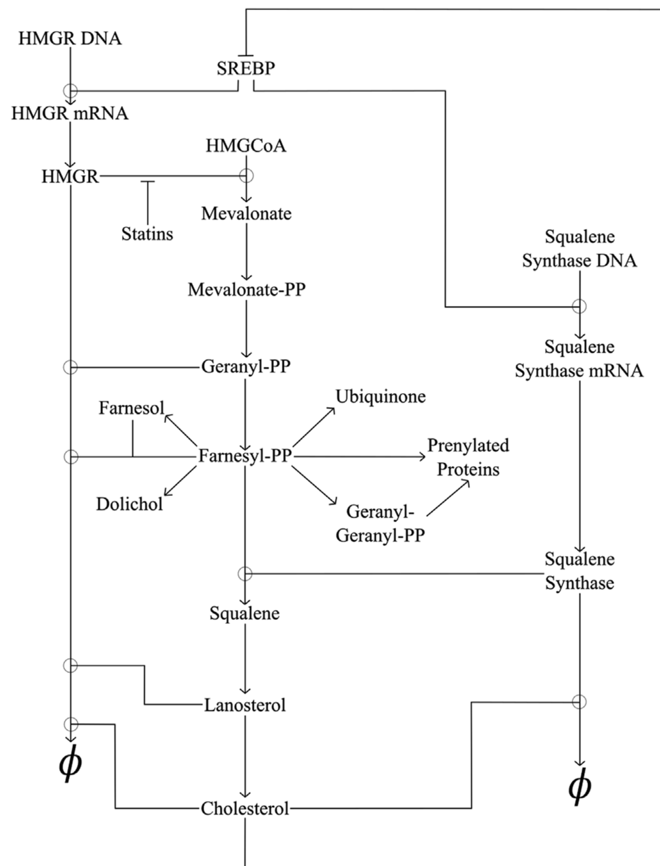


Fig. 8. *Diagram of the Mevalonate pathway, adapted from (*Pool et al. 2018*).* Arrows show the forward reactions, the circles denote enhancement of the reaction and the bar denotes inhibition. Through the inhibition of sterol regulatory element-binding protein (SREBP) (via cholesterol) and enhancement of degradation of enzymes (3-hydroxy-3-methylglutary coenzyme A reductase (HMGR) and Squalene Synthase, the products of the mevalonate pathway are tightly regulated. HMGCoA, 3-hydroxy-3-methylglutaryl-CoA; PP, pyrophosphate; φ, degradation/use in other biological process.

medically relevant outcome (Sekula et al., 2016; Smith and Ebrahim, 2003).

In the first study by Burgess and Davey Smith, a two-sample Mendelian randomization analysis was performed using published data of 16,144 advanced AMD cases (neovascularisation or GA) and 17,832 controls predominantly of European ancestry (Burgess and Davey Smith, 2017). The authors analyzed 185 variants previously found to be associated with LDL-C, HDL-C or TG in GWAS. In total, 9 variants were associated with AMD risk after adjusting for multiple testing ($P < 0.0003$). The authors concluded that the results of the Mendelian randomization analysis show evidence of a causal role of long-term elevated levels of plasma HDL-C in increasing AMD risk, with an OR of 1.22 (95% confidence interval [CI], 1.03–1.44, $P = 0.02$) per 1 standard deviation increase in HDL-C. No evidence of causal effect of LDL-C or TG was detected (OR = 0.94 (0.82–1.09), $P = 0.41$ for LDL; 0.85 (0.67–1.07), $P = 0.16$ for triglycerides). Interestingly, the three variants most strongly associated with AMD, one in the *CETP* and two in the *LIPC* gene regions, have opposite effects on circulating HDL levels. The *CETP* variant associated with higher HDL level was correlated with increased AMD risk, while *LIPC* variants associated with lower HDL were also correlated with increased AMD risk. Moreover, the variant associated with the highest HDL level (rs5880 in the *CETP* gene region) was not associated with AMD risk after correction for multiple testing. Taken together, this study suggests that not all mechanisms for increasing circulating HDL concentration increase AMD risk uniformly. As alternative interpretation, the variants may have a local effect on the lipid metabolism in the retina (section 5.2), and the association with circulating HDL is due to the effect on other tissues that express these genes and are known to regulate HDL circulating levels, like the liver. This local effect on retina lipid metabolism is also suggested by the very high cholesterol load in photoreceptors and the expression of the genes in the retina (see section 5).

In the second study, a Mendelian randomization analysis for causal role of lipids in advanced AMD was performed in the same multiethnic populations comprising 16,144 advanced AMD cases and 17,832 controls of European descent, together with 2219 cases and 5275 controls of Asian descent (Fan et al., 2017). The analysis confirmed a causal role for plasma HDL-C in AMD but not for LDL-C or TG. In addition, the OR was higher for the Asian than the European population. Like the previous model, this study also found that *CETP* and *LIPC* variants associated with higher HDL have opposite effects on AMD.

5. Lipoprotein metabolism in the outer retina

As shown in section 3.1 the association of systemic lipids, in particular HDL-C, with AMD, produced conflicting results. Mendelian randomization studies confirmed a causal role for elevated levels of circulating HDL cholesterol in AMD risk. However, not all mechanisms for increasing circulating HDL concentrations increase AMD risk uniformly, suggesting that the genetic variations also contribute to these inconsistencies (section 4.2). There are several AMD-associated variants reside in or near genes of the lipoprotein metabolism (section 4.1). Most of these genes are also expressed locally in the outer retina where AMD initiates, suggesting that the disease mechanisms of the genetic variants may rather be attributed to an effect on the local lipoprotein metabolism. In this section, we review the current literature on the uptake of circulating lipoproteins and local synthesis and trafficking of lipids in the outer retina.

5.1. Uptake of circulating lipoproteins by the outer retina

Lipoproteins are transported from the choroid to the photoreceptors through the RPE. The RPE is composed of polarized cells that express two types of receptors for lipoprotein uptake. The first are receptors specific for very low-density lipoprotein cholesterol (VLDL-R) (Hu et al., 2008) and low-density lipoprotein cholesterol (LDL-R) (Gordiyenko et al., 2004; Hayes et al., 1989; Tserentsoodol et al., 2006b). The second group includes cluster of differentiation 36 (CD36) scavenger receptor (Kociok and Joussen, 2007; Ryeom et al., 1996) and scavenger receptors BI and BII (SR-BI and SR-BII) (Duncan et al., 2002, 2009; Tserentsoodol et al., 2006a). Scavenger receptors take up negatively charge macromolecules without specificity. LDL-R and CD36 are localized to the basement membrane of the RPE. With these receptors RPE cells internalize considerable amounts of LDL-C and less efficiently HDL-C from the choroidal circulation (Elner, 2002; Gordiyenko et al., 2004; Haimovici et al., 1997). PUFAs, such as DHA and gamma-linolenic acid (GLA), are also taken up into the RPE from the circulation (Schnebelen et al., 2009; Wang and Anderson, 1993) by the major facilitator superfamily domain-containing protein 2 (MFSD2A) transporter (Wong et al., 2016). This clearly indicate that dietary lipids (section 2.1) can be taken up by the outer retina. As SR-BII is localized at the apical surface, it takes up lipids from the sub retinal space into the RPE (Fig. 8) (Duncan et al., 2002, 2009; Tserentsoodol et al., 2006a). CD36 also contributes to internal cholesterol levels by playing a role in the shedding of disk membranes and signaling engulfment, known as phagocytosis (Ryeom et al., 1996) in which the cholesterol content (as well as retinoids and opsins) of disk membranes are degraded or recycled.

Into photoreceptors lipid uptake occurs through LDL-R localized to the inner segments (Tserentsoodol et al., 2006b), SR-BI and SR-BII that are present in photoreceptor outer segments adjacent to the connecting

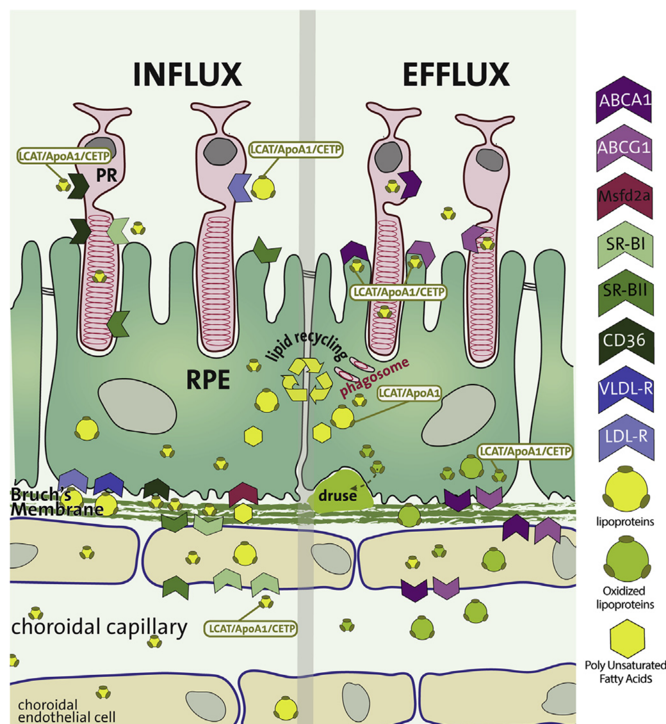


Fig. 9. *Lipid transport in the retina.*
Besides general anabolic and catabolic lipid metabolism taking place in the retina, the retinal pigment epithelium (RPE) functions as transfer site for lipids and lipoprotein particles (yellow and green spheres) from the circulation represented by the choroidal capillaries to the photoreceptors (PR), and vice versa. On the left hand side the import of lipids via the RPE to the photoreceptors is shown. The required receptors and their location are outlined by arrow symbols indicating the direction of transport. SR-BI scavenger receptors BI, SR-BII scavenger receptors BII, CD36 cluster of differentiation 36, LDL-R LDL receptors, VLDL-R VLDL receptors. In case of polyunsaturated fatty acids (PUFA) like decosahexanoic acid the MFSD2A receptor has been reported (Wong et al., 2016). On the right hand side the efflux of lipids and the involved receptors are shown. ABCA1 ATP binding cassette subfamily A member 1, ABCG1 ATP-binding cassette sub-family G member 1. The RPE cells are recycling a substantial amount of lipids, which are continuously provided through phagocytosed membrane discs of the photoreceptor outer segments. However, oxidized lipid species (oxi) are either exported into the circulation as newly assembled lipoprotein particles (green spheres) or deposited into the basal extracellular space, eventually forming drusen, which could lead to pathology. LCAT, lecithin-cholesterol acyltransferase; APOA1, apolipoprotein A1; CETP, cholesteryl ester transfer protein.

cilium (Tserentsoodol et al., 2006a) and CD36 that is localized to the inner and outer segments of the rod photoreceptors, but not of cones (Calvo et al., 1998).

5.2. Local synthesis and trafficking of lipids

Apart from uptake from the systemic circulation many mammalian cells, such as RPE and photoreceptors, also synthesize their own cholesterol via the mevalonate pathway (Buhaescu and Izzedine, 2007; Fliesler and Bretillon, 2010) (Figs. 8 and 9). There is a tight regulation of the intracellular cholesterol concentrations via several negative feedback mechanisms. These include the regulation of 3-hydroxy-3-methylglutary coenzyme A reductase HMGR, squalene synthase and LDL-Rs, all of which are under the control of the transcription factor Sterol Regulatory Element-Binding Protein (SREBP) (Srivastava et al., 1995).

At normal cellular cholesterol concentrations SREBP is localized to the endoplasmic reticulum When cellular cholesterol concentrations decrease, SREBP moves to the Golgi where it is cleaved. The amino terminal domain of the cleaved SREBP enters the nucleus where it activates target genes (Edwards et al., 2000) like the gene for HMGR. At low cellular cholesterol concentrations, the *HMGR* mRNA is translated into an enzyme that initiates a cascade of approximately 37 enzymatic reactions leading to the production of geranyl-PP, farnesyl-PP (Foresti et al., 2013), lanosterol (Pool et al., 2018)and cholesterol (Brown and Goldstein, 1980; Mazein et al., 2013). Once the level of these molecules increases they can initiate and accelerate *HMGR* degradation as a negative feedback. In addition, as a response to changes in cholesterol concentration squalene synthase degradation is accelerated to stop cholesterol over production. It is important to mention that the RPE also expresses a comprehensive set of enzymes that are involved in synthesis and remodeling of sphingomyelins and ceramides (Zhu et al., 2010). Some sphingomyelinases, such as sphingomyelin phosphodiesterase 3 and sphingosine kinase 1, have shown to function as Yin and Yang in RPE cells regarding cell death and proliferation thus their dysregulation is closely linked to retinal degeneration (Abrahan et al., 2010).

Because lipids are insoluble in water, they are packaged into lipoprotein particles, consisting of an amphipathic lipid monolayer covering a core of hydrophobic lipids (Brunham and Hayden, 2015). In the initial phase of lipoprotein construction apolipoproteins combine with cholesterol, triglycerides and phospholipids to create a nascent lipoprotein. Packaging of lipids is facilitated by plasma proteins lecithin-cholesterol acyltransferase (LCAT), CETP (Small, 1988) and phospholipid transfer protein (PLTP), that promotes the maturation of HDL in the cells. Nascent HDL matures by accumulating more lipids into the core of the lipoprotein (Gruffat et al., 1996). The role of LCAT is to convert free cholesterol into cholesterol esters, which are then sequestered into nascent HDL, producing fully mature HDL particles, while CETP transfers cholesterol esters and triglycerides from HDL to LDL and VLDL particles (de Grooth et al., 2004). LCAT is localized to photoreceptor outer segments, RPE and choriocapillaris, and CETP to photoreceptor outer segments and the choriocapillaris (Tserentsoodol et al., 2006a). A marker protein for HDL is APOA1. APOA1 can be detected in the choriocapillaris, RPE, photoreceptor outer and inner segments (Tserentsoodol et al., 2006a). Notably, genetic variants in several of these proteins (CETP, APOA1), have been associated with AMD (section 4).

5.3. Efflux of lipids from the outer retina

With cholesterol influx through receptors and phagocytosis and synthesis from the mevalonate pathway, the cells regulates cholesterol homeostasis via cholesterol efflux. The RPE secretes lipoprotein like particles (LLP) back to the circulation through the Bruch's membrane. The characterization of LLP from intraocular origin in the Bruch's membrane showed that these are distinct from circulating plasma lipoproteins (Li et al., 2005). The particles are grouped into two fractions; a large peak with plasma LDL-HDL density range, containing phospholipid and unesterified cholesterol, and a small peak with plasma VLDL density range, containing esterified cholesterol, both peaks contained APOA1, the primary apolipoprotein of HDL, and apolipoprotein B (APOB), the primary apolipoprotein of LDL and VLDL. Although the particles are distinct from circulating plasma lipoproteins, it is likely that they diffuse through Bruch's membrane in the same way for removal into the circulation, perhaps via the LDLR (that bind to ApoB) on the surface of the choriocapillaris (Koo et al., 2014; Tserentsoodol et al., 2006b; Whitehead et al., 2006). It has been suggested that Bruch's membrane LLPs (BrM-LLP) represent a major portion of lipids found in Bruch's membrane (Huang et al., 2007). Profiling the BrM-LLP, it was found that esterified cholesterol was the largest component of BrM-LLP lipids, over 10-fold more abundant than triglyceride (Wang et al., 2009). It was suggested that this abundance of esterified cholesterol could contribute to a transport barrier in aging (Curcio et al., 2011). It is unknown why this function becomes

deranged with age but some suggestions are the balance between removal and production of lipoproteins in the retina becomes unbalanced with age – leading to the accumulation of esterified choelsterol. The accumulation of esterified cholesterol over time might decrease the permiability of Bruch's membrane exaserbating the accumulation, until a critical threshold is reached and depositions start to form. Or finally, perhaps the accumulation might not be a problem on its own, but when combined with other risk factors (for example abberant CETP), problems start to arise.

Due to insolubility, lipids are exported in a complex with lipoproteins via the ABCA1 transporter (Fitzgerald et al., 2004; Yokoyama, 2005). ABCA1 is localized to the basal and apical membrane of the RPE and photoreceptor inner and outer segments (Ananth et al., 2014; Tserentsoodol et al., 2006a) (Fig. 9). A related ATP-binding cassette transporter, ABCG1, is present in RPE where protein levels appear to be higher at the apical than basal membranes, and the ABCG1 protein also present on the photoreceptor outer segment (Ananth et al., 2014; Ye et al., 2011) (Fig. 9). It is important to note that the receptors related to HDL lipoproteins described here may be serving multiple role within the same environment (Koo et al., 2014). There may be a combined role for the uptake of HDL lipoproteins and the xanthophylls carried by HDL. Lutein and zeaxanthin may protect against AMD through the filtering of blue light and anti-oxidant activities (Whitehead et al., 2006).

5.4. Shuttling of lipids in the interphotoreceptor matrix

As we have seen, the RPE is responsible for the careful balance of processing lipids, such as esterfied cholesterol, phospholipids, free cholesterol and triglycerides, internalized from the extracellular space and secreting lipids back into the extracellular milieu. In the interphotoreceptor matrix (IPM) lipoprotein particles can mature by taking up additional lipids with the help of resident LCAT, PLTP and CETP, making them ready for uptake by the scavenger receptors on photoreceptors. Therefore, lipoproteins, especially HDL, in the IPM play a role not just in reverse cholesterol transport but as a shuttling service between the RPE and photoreceptors for the highly insoluble lipid molecules. This is essential as cholesterol is required to stabilize rhodopsin (Albert et al., 1996a). However, high concentration of cholesterol can also inhibit rhodopsin activation (Albert et al., 1996a). The interphotoreceptor retinoid-binding protein can bind two retinoids, as storage or transport from RPE to photorecepor outer segments and visa versa (Chen et al., 1996). Long fatty acids interfere with the retinoid binding (Chen et al., 1993), DHA specifically modulates the interaction with 11-*cis*-retinal (Chen et al., 1996). There is a gradient of DHA between the photorecepor outer segments and RPE, which might influence the transportation of retinoids (Chen et al., 1996). Photoreceptor disk membranes are synthesized at the base of the rod photoreceptor, adjacent to the cilium (Burgoyne et al., 2015). The process is continuous with the membrane infolding to create the disks, pushing the older disks towards the apex of the photoreceptor over several days. Approximately 10% of the total membrane are newly synthesized each day (Boesze-Battaglia and Goldberg, 2002), and newly synthesized disk membranes contain 6-fold more cholesterol than the oldest disks at the tip of the photoreceptor (Albert and Boesze-Battaglia, 2005). The production of this amount of membrane each day requires a very high turnover of cholesterol and supports the need for the shuttling process (Young, 1971). Differences in lipid and fatty acid composition between the plasma membrane and disk membrane composition can provide insight into the roles of cholesterol and fatty acids in the rhodopsin cycle. The most prominent difference is in DHA (22:6) concentrations which account for 35% of the total disk membrane, but 5% in plasma membrane (Boesze-Battaglia and Schimmel, 1997; Lamba et al., 1994). While there is no location-related change in fatty acid or phospholipid composition in the disk membranes, the cholesterol content decreases from the base to the apical tip as cholesterol relocates to the plasma membrane over the lifetime of the disk (Boesze-Battaglia et al., 1989, 1990). It has been shown that the plasma membrane contains three times as much cholesterol as the disk membranes and recent studies (Albert et al., 1996a, 1996b) suggested that cholesterol interacts directly with and stabilizes rhodopsin, while DHA has been implicated in rhodopsin regeneration - rhodopsin regenerates faster in the DHA-rich disk membranes than the plasma membranes (Bush et al., 1991). Thus the composition allows for functional regulation of rhodopsin - storage in the photoreceptor, without activation, until it is required whereupon its translocation to the disk membranes can be regenerated quickly.

In summary, although 70% of the lipids needed for normal function is synthesized locally (Lin et al., 2016), there is still a clear associations between circulating and retinal tissue levels of lipids (Acar et al., 2012; Gorusupudi et al., 2016; Zheng et al., 2015).

6. Model systems for lipid metabolism

As explained in previous sections, how systemic and locally synthesized lipids are involved in the development and progression of AMD is not fully understood. Most studies in lipid metabolisms use different model systems. This section will summarize the current knowledge collected using *in vivo* and *in vitro* models with a potential to be used for modelling the contribution of lipid metabolism to AMD.

6.1. Plasma lipoproteins profiles in different animal models

Many laboratories use different animal models, in particular those developed for dyslipidemia studies (Gistera and Hansson, 2017; Wang et al., 2010; Yin et al., 2012), to understand how changes in lipids contribute to diseases. However, to translate animal research to human it is imperative to characterize and compare lipid levels to humans. Humans have a high LDL-C and low HDL-C profile (Table 1), which is referred to as a 'human-like profile' and as such animal studies aim to replicate these values (Yin et al., 2012). In a comprehensive study on dyslipidemia the lipid profiles of 24 commonly used animal models were analyzed (Yin et al., 2012). In addition, several, less comprehensive, studies examined some but not all aspect of lipids profiles which is summarized in Table 3.

When non-human primates were examined, most had similar lipoproteins profiles compared to healthy human except marmoset that had higher TG level (Yin et al., 2012). Dyslipidemic African green monkey, rhesus monkey with metabolic syndrome, diabetic rhesus monkey and rhesus monkey with diet-induced obesity models' lipoproteins profiles were comparable to human dyslipidemia (Table 1) (Hals et al., 2017; Yin et al., 2012). Non-human primates responded to anti-dyslipidemic agent simvastatin like human. Therefore, non-human primates are suitable to study human conditions, however, these experiments are expensive and face many challenges (Martin, 2008). As a note, McGill et al. conducted *in vivo* experiments on rhesus monkeys, and studied the effect of omega-3 FAs (McGill et al., 2016). They found increased fundus autofluorescence in monkeys kept on omega-3 FA deficient diet.

Pigs, dogs, mice and rats normally have low or no CETP activity, high HDL-C and low LDL-C plasma lipoprotein levels (Ajadi et al., 2016; Downs et al., 1993; Usui et al., 2014), which is opposite to human (Table 1). Ishikawa et al. showed significant differences in cholesteryl ester (CE), phosphatidylethanolamine (PE), ether-type phosphatidylcholine and PE, phosphatidylinositols, LPC, Coenzyme Q, diacylglycerol (DAG), and Sulfatides when humans profiles were compared to New Zealand white rabbits, BALB/c mice or Sprague-Dawley rats (Ishikawa et al., 2015). In addition, in rabbits, hepatic lipase is absent, which results in cholesterol accumulation in chylomicron residues and beta-VLDL-C lipoprotein particles (Yin et al., 2012). Gottingen mini pigs and obese beagles have human-like omega-6 pathway-related fatty acids and nonessential fatty acids fractions (Morishita et al., 2016; Yin et al., 2012), but their basal plasma lipid levels are different from humans due to their low CETP activity, still their response to simvastatin treatment was similar to human (Jeusette et al., 2005; Yin et al., 2012).

Table 3
Comparison of plasma lipid profiles of different species to "human-like profile".

Model system	Basal Plasma Lipid Levels (mg/dl)						Plasma Lipid Fractions (nmol/ml)
	CETP	TG	TC	VLDL-C	LDL-C	HDL-C	CE
Human (Quehenberger et al., 2010; Yin et al., 2012)	Yes	> 150	> 200	> 30	> 100	35–40	3600
Dyslipidemic human (Yin et al., 2012)	Yes	154 ± 15	226 ± 6	N/A	154 ± 7	48 ± 4	2912 ± 110
Dyslipidemic African Green (Yin et al., 2012)	Yes	52 ± 10	336 ± 51	33 ± 10	210 ± 36	92 ± 7	N/A
African Green (Jorgensen et al., 2013; Yin et al., 2012)	Yes	54 ± 3	134 ± 5	4 ± 1	71 ± 3	59 ± 4	2557 ± 131
Cynomolgus (Hals et al., 2017; Yin et al., 2012; Yue et al., 2016)	Yes	60 ± 8	139 ± 13	5 ± 2	66 ± 9	67 ± 5	2023 ± 223
Rhesus (Graham et al., 2013; Li et al., 2013; Yin et al., 2012)	Yes	42 ± 3	120 ± 5	4 ± 1	59 ± 3	58 ± 5	N/A
Rhesus, Metabolic syndrome (Yin et al., 2012)	Yes	118 ± 13	159 ± 12	9 ± 1	85 ± 7	65 ± 7	2867 ± 315
Rhesus, diabetic (Yin et al., 2012)	Yes	192 ± 35	194 ± 18	22 ± 6	99 ± 7	62 ± 11	3239 ± 462
Rhesus, diet-induced obesity (Graham et al., 2013; Li et al., 2013; Yin et al., 2012)	Yes	179 ± 31	131 ± 13	12 ± 1	68 ± 9	51 ± 7	2189 ± 97
Baboon (Shi et al., 2013)	Yes	47	102	N/A	43	59	N/A
Baboon High-fat diet (Shi et al., 2013)	Yes	49	209	N/A	113	97	N/A
Marmoset (Yin et al., 2012)	Yes	363 ± 134	161 ± 16	25 ± 11	77 ± 9	58 ± 10	2824 ± 168
Pig (Gunness et al., 2016; Komprda et al., 2016; Yin et al., 2012)	No	32 ± 2	96 ± 7	5 ± 0.4	39 ± 4	52 ± 3	1613 ± 103
LDL-r KO pig (Li et al., 2016; Ogita et al., 2016)	No	43.2 ± 10.1	602.3 ± 104.4	N/A	510.0 ± 86.1	24.5 ± 7.45	N/A
Dog (Ajadi et al., 2016; Downs et al., 1993; Mori et al., 2015; Usui et al., 2014; Yin et al., 2012)	Yes	98 ± 15	196 ± 6	7 ± 2	26 ± 3	163 ± 3	3463 ± 148
Rabbit (Casamassima et al., 2017; Ishikawa et al., 2015; Lin et al., 2017; Yin et al., 2012)	Yes	47 ± 5	29 ± 1	4 ± 0.3	8 ± 0.4	18 ± 1	518 ± 23
Rabbit (Cholesterol fed diet) (Casamassima et al., 2017; Lin et al., 2017; Yin et al., 2012)	Yes	48 ± 4	811 ± 48	439 ± 26	317 ± 24	44 ± 4	10599 ± 797
Hamster (Huang et al., 2016; Yin et al., 2012)	Yes	226 ± 11	141 ± 7	16 ± 1	31 ± 2	94 ± 6	2087 ± 116
Hamster High-fat diet (Huang et al., 2016; Yin et al., 2012)	Yes	534 ± 43	184 ± 4	35 ± 2	39 ± 3	110 ± 3	2419 ± 112
Rat (Graham et al., 2013; Ishikawa et al., 2015; Komprda et al., 2016; Yin et al., 2012)	No	85 ± 2	98 ± 4	10 ± 0.3	36 ± 3	53 ± 1	1608 ± 62
Rat High-fat diet (Yin et al., 2012)	No	1482 ± 210	148 ± 8	62 ± 7	20 ± 2	66 ± 2	1612 ± 79
BALB/c mice (Ishikawa et al., 2015; Wang et al., 2014)	No	≈1.3 mmol/l	≈3.2 mmol/l	N/A	≈0.12 mmol/l	≈2.5 mmol/l	N/A
C57BL/6J (Graham et al., 2013; Liu et al., 2017; Sallo et al., 2009; Yin et al., 2012)	No	130 ± 10	127 ± 4	8 ± 1	21 ± 2	97 ± 4	2267 ± 60
db/db (Noratto et al., 2017; Yin et al., 2012)	No	308 ± 16/ 46.5 ± 7.0	170 ± 5/ 138.5 ± 13.7	13 ± -1	30 ± 2/92.4 ± 12	126 ± 4/46 ± 5.5	3105 ± 105
ApoE KO (Stoger et al., 2016; Yin et al., 2012; Zheng et al., 2016)	No	102 ± 14	412 ± 21	226 ± 17	178 ± 13	8 ± 1	7144 ± 686
ApoE KO (Cholesterol fed diet) (Stoger et al., 2016; Yin et al., 2012)	No	154 ± 31	629	205	402	22	18854 ± 580
ldlr KO (Graham et al., 2013; Liang et al., 2012; Yin et al., 2012)	No	124 ± 8	250 ± 8	13 ± 1	168 ± 5	69 ± 3	3672 ± 109
ldlr KO (Cholesterol fed diet) (Yin et al., 2012)	No	404 ± 35	1677 ± 98	904 ± 47	761 ± 57	12 ± 2	21577 ± 1192
ApoE/LDL-r KO (Kostogrys et al., 2017)	No	3.53 ± 1.16	33.13 ± 4.59	N/A	13.74 ± 1.76	0.86 ± 0.09	N/A
LCAT KO (Lambert et al., 2001)	No	74 ± 4	76 ± 2	N/A	N/A	70 ± 2	N/A
Fat1 transgenic (Kang, 2007; Kim et al., 2012)	No	49 ± 5	45 ± 4	11 ± 1	6 ± 3	37 ± 3	N/A
ApoB100 transgenic (Sallo et al., 2009)	No	N/A	3.4 mmol/l	N/A	1.4 mmol/l	N/A	N/A
ApoB100 transgenic (Cholesterol fed diet) (Sallo et al., 2009)	No	N/A	5.0 mmol/l	N/A	2.7 mmol/l	N/A	N/A
Biglycan transgenic (Sallo et al., 2009)	No	N/A	2.5 mmol/l	N/A	1.0 mmol/l	N/A	N/A

(*continued on next page*)

Table 3 (*continued*)

Model system	Basal Plasma Lipid Levels (mg/dl)						Plasma Lipid Fractions (nmol/ml)
	CETP	TG	TC	VLDL-C	LDL-C	HDL-C	CE
Biglycan transgenic (Cholesterol fed diet) (Sallo et al., 2009)	No	N/A	2.6 mmol/l	N/A	1.6 mmol/l	N/A	N/A
ApoB-100/biglycan transgenic (Sallo et al., 2009)	No	N/A	3.1 mmol/l	N/A	1.2 mmol/l	N/A	N/A
ApoB-100/biglycan transgenic (Cholesterol fed diet) (Sallo et al., 2009)	No	N/A	4.9 mmol/l	N/A	2.1 mmol/l	N/A	N/A
ApoB100 transgenic/LDL-r KO (Chevrier et al., 2015)	No	≈2.1 mmol/l	N/A	N/A	≈9 mmol/l	N/A	N/A
Apoee2/e3/e4 transgenic (Malek et al., 2005)	No	N/A	70–180	N/A	N/A	N/A	N/A
Apoe3-Leiden transgenic (van den Maagdenberg et al., 1993)	No	2.06 ± 0.90	4.27 ± 1.16	N/A	N/A	N/A	N/A
CETP transgenic/ldlr KO (Graham et al., 2013; Hime et al., 2008; Yin et al., 2012)	Yes	67 ± 9	89 ± 4	10 ± 2	41 ± 2	37 ± 4	1528 ± 65
CETP transgenic/ldlr KO (Cholesterol fed diet) (Yin et al., 2012)	Yes	59 ± 6	202 ± 4	51 ± 4	96 ± 4	54 ± 3	3332 ± 125

Model system	Plasma Lipid Fractions (nmol/ml)						
	DAG	FFA	TAG	LPC	PC	PE	FC
Human (Quehenberger et al., 2010; Yin et al., 2012)	39	214	1058	103	1974	435	700
Dyslipidemic human (Yin et al., 2012)	31 ± 2	352 ± 22	1263 ± 84	208 ± 6	1861 ± 67	184 ± 8	1355 ± 47
Dyslipidemic African Green (Yin et al., 2012)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
African Green (Jorgensen et al., 2013; Yin et al., 2012)	45 ± 8	581 ± 62	501 ± 42	211 ± 12	1813 ± 65	233 ± 14	1128 ± 102
Cynomolgus (Hals et al., 2017; Yin et al., 2012; Yue et al., 2016)	22 ± 2	351 ± 58	510 ± 92	248 ± 11	1706 ± 138	235 ± 15	794 ± 67
Rhesus (Graham et al., 2013; Li et al., 2013; Yin et al., 2012)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rhesus, Metabolic syndrome (Yin et al., 2012)	45 ± 3	791 ± 81	921 ± 103	212 ± 12	2186 ± 110	228 ± 12	1238 ± 158
Rhesus, diabetic (Yin et al., 2012)	87 ± 15	1068 ± 124	1851 ± 308	252 ± 21	2513 ± 206	296 ± 33	1766 ± 314
Rhesus, diet-induced obesity (Graham et al., 2013; Li et al., 2013; Yin et al., 2012)	48 ± 6	374 ± 28	1554 ± 268	219 ± 7	2382 ± 99	233 ± 15	1042 ± 46
Baboon (Shi et al., 2013)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Baboon High-fat diet (Shi et al., 2013)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Marmoset (Yin et al., 2012)	123 ± 30	473 ± 61	2880 ± 754	304 ± 20	2794 ± 254	285 ± 32	1447 ± 142
Pig (Gunness et al., 2016; Komprda et al., 2016; Yin et al., 2012)	26 ± 2	105 ± 4	344 ± 22	219 ± 8	1034 ± 77	79 ± 5	450 ± 34
LDL-r KO pig (Li et al., 2016; Ogita et al., 2016)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Dog (Ajadi et al., 2016; Downs et al., 1993; Mori et al., 2015; Usui et al., 2014; Yin et al., 2012)	38 ± 5	947 ± 102	787 ± 131	333 ± 14	4056 ± 230	189 ± 10	1350 ± 53
Rabbit (Casamassima et al., 2017; Ishikawa et al., 2015; Lin et al., 2017; Yin et al., 2012)	19 ± 1	159 ± 11	339 ± 27	210 ± 5	507 ± 23	110 ± 5	294 ± 24
Rabbit (Cholesterol fed diet) (Casamassima et al., 2017; Lin et al., 2017; Yin et al., 2012)	23 ± 1	269 ± 10	154 ± 11	499 ± 22	1646 ± 123	224 ± 16	3494 ± 364
Hamster (Huang et al., 2016; Yin et al., 2012)	39 ± 2	209 ± 8	2255 ± 119	705 ± 24	2836 ± 192	233 ± 9	1005 ± 68
Hamster High-fat diet (Huang et al., 2016; Yin et al., 2012)	73 ± 7	431 ± 18	3234 ± 268	864 ± 26	3563 ± 192	261 ± 14	1360 ± 58
Rat (Graham et al., 2013; Ishikawa et al., 2015; Komprda et al., 2016; Yin et al., 2012)	35 ± 3	417 ± 21	847 ± 15	541 ± 8	1192 ± 46	173 ± 8	769 ± 49
Rat High-fat diet (Yin et al., 2012)	193 ± 23	747 ± 32	15411 ± 2293	892 ± 47	4202 ± 354	404 ± 20	2582 ± 235
BALB/c mice (Ishikawa et al., 2015; Wang et al., 2014)	N/A	N/A	N/A	N/A	N/A	N/A	N/A

(*continued on next page*)

Table 3 (*continued*)

Model system	Plasma Lipid Fractions (nmol/ml)						
	DAG	FFA	TAG	LPC	PC	PE	FC
C57BL/6J (Graham et al., 2013; Liu et al., 2017; Sallo et al., 2009; Yin et al., 2012)	51 ± 8	557 ± 25	1078 ± 83	843 ± 21	2130 ± 70	252 ± 9	794 ± 32
db/db (Noratto et al., 2017; Yin et al., 2012)	60 ± 4	1028 ± 81	2558 ± 157	967 ± 19	2536 ± 31	353 ± 11	929 ± 33
ApoE KO (Stoger et al., 2016; Yin et al., 2012; Zheng et al., 2016)	58 ± 6	549 ± 61	845 ± 115	668 ± 62	1930 ± 246	247 ± 20	3487 ± 446
ApoE KO (Cholesterol fed diet) (Stoger et al., 2016; Yin et al., 2012)	51 ± 4	566 ± 19	692 ± 58	1170 ± 25	4391 ± 104	446 ± 14	10176 ± 230
ldlr KO (Graham et al., 2013; Liang et al., 2012; Yin et al., 2012)	39 ± 4	538 ± 69	1032 ± 62	820 ± 21	2608 ± 85	320 ± 16	1703 ± 55
ldlr KO (Cholesterol fed diet) (Yin et al., 2012)	65 ± 3	684 ± 33	2814 ± 294	1733 ± 84	5953 ± 292	581 ± 32	9829 ± 513
ApoE/LDL-r KO (Kostogrys et al., 2017)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LCAT KO (Lambert et al., 2001)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fat1 transgenic (Kang, 2007; Kim et al., 2012)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ApoB100 transgenic (Sallo et al., 2009)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ApoB100 transgenic (Cholesterol fed diet) (Sallo et al., 2009)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biglycan transgenic (Sallo et al., 2009)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Biglycan transgenic (Cholesterol fed diet) (Sallo et al., 2009)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ApoB-100/biglycan transgenic (Sallo et al., 2009)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ApoB-100/biglycan transgenic (Cholesterol fed diet) (Sallo et al., 2009)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ApoB100 transgenic/LDL-r KO (Chevrier et al., 2015)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Apoee2/e3/e4 transgenic (Malek et al., 2005)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Apoe3-Leiden transgenic (van den Maagdenberg et al., 1993)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CETP transgenic/ldlr KO (Graham et al., 2013; Hime et al., 2008; Yin et al., 2012)	27 ± 2	581 ± 38	557 ± 76	555 ± 19	1190 ± 46	166 ± 3	538 ± 16
CETP transgenic/ldlr KO (Cholesterol fed diet) (Yin et al., 2012)	34 ± 5	716 ± 85	491 ± 51	626 ± 16	1688 ± 35	207 ± 9	1187 ± 29

CETP, cholesteryl ester transfer protein; CE, cholesteryl ester; DAG, diacylglycerol; FFA, free fatty acids; db/db, obese diabetic; FC, free cholesterol; HDL-C, high-density lipoprotein cholesterol; KO, knock-out; LCAT, Lecithin Cholesterol Acyltransferase; LDL-C, low-density lipoprotein cholesterol; LPC, lysophophatidylcholine; N/A, not available; PC, phosphatidylcholine; PE, phosphatidylethanolamine; TAG, triacylglycerol; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

Overall, these animal models are suitable to study some, but not all aspects of human lipid metabolism (Table 3).

6.2. Genetically modified animal models for lipid metabolism with/without eye research

Although mice or pig models are not ideal to study human lipid metabolism, genetically modified strains that change plasma lipid profiles are widely used in eye research especially when animals are fed on a high fat diet (Al-Mashhadi et al., 2013; Davis et al., 2014; Pennesi et al., 2012; Yin et al., 2012). In general, *Apob+/-*, *Apoe−/− Ldlr−/−*, *Cetp+/- Ldlr−/−*, *Apoe3-Leiden* and *Apob+/-,biglycan+/--*,transgenic mice models still have low or mildly elevated TC and LDL-C when kept on normal chow (van den Maagdenberg et al., 1993; Yin et al., 2012). However, under high cholesterol diet, TC and LDL-C levels were similar to the 'human-like profile' (Davis et al., 2014; Pennesi et al., 2012; Yin et al., 2012). In the *Apob+/-*,mice, in which the drusen-specific human APOB100 is overexpressed in the RPE, but not the choroidal endothelium, synthesizes and secretes APOB100 protein (Fujihara et al., 2014). In the *Apob+/-biglycan+/-*transgenic mice Sallo et al. showed increased lipid deposition and thickened Bruch's membrane (Sallo et al., 2009) suggesting that these 'humanized mice' can mimic some aspects of AMD pathology. *Apoe−/−*, *Apoe3-Leiden* and *Ldlr−/−* mice also showed Bruch's membrane thickening, presence of membrane-bound material and development of basal laminar-like deposits (Dithmar et al., 2000; Kliffen et al., 2000; Rudolf et al., 2004). In *Apoe2/e3/e4* transgenic animals, where only plasma cholesterol was measured (Table 1), amyloid B accumulation was observed in the retina (Ding et al., 2011). However, while in humans the *APOE4* allele is correlated with protection from the development of AMD, in these mice the opposite appears to be true (Malek et al., 2005; Pennesi et al., 2012). Although plasma levels of cholesterol, triacylglycerol, and lipoproteins in the *Vldl−/−* mice was similar to wild-type strains, these models develop a retinal neovascularisation-like phenotype starting at 2 weeks of age (Chen et al., 2007).

Several other genetically modified mouse strains have been generated specifically for studying lipid metabolism in AMD, but were not analyzed for plasma lipid levels (for review see (Pennesi et al., 2012)). Complement factor H knockout (*Cfh−/−*) animals showed a thinning of Bruch's membrane (Coffey et al., 2007) when the animals were raised on normal chow. However, Toomey et al. showed that when these animals were raised on high cholesterol diet there was an increased accumulation of sub-RPE deposits, suggesting a role for CFH in regulation of lipoprotein binding in the sub-RPE space (Toomey et al., 2015). The potential relevance of fatty acids in AMD were examined in the *Abca4−/− Rdh8−/−* mouse model (Orban et al., 2015; Yin et al., 2012). In this model, light-induced retinal degeneration resulted a decrease in DHA levels, that may mimic the decreased serum DHA levels in AMD (Handa et al., 2017; Orban et al., 2015). CD36, the main receptor for oxidized lipids, expressed on basolateral sides on RPE cells, microvascular endothelial cells and photoreceptors, and its expression is inversely correlated with AMD (Kondo et al., 2009). *Cd36−/−* mice are characterized by a progressive age-dependent photoreceptor cell death with an increased plasma oxidized LDL-C level (20 ng/ml) and sub-RPE deposit formation (Picard et al., 2010). A mutant mouse that express human APOA and human APOB100 to generate authentic Lp(a) particles but has a defective oxidized lipid binding site (LBS) (mutant LBS- Lp(a) mice), showed sub-RPE deposit accumulation and RPE degeneration when raised on high fat diet (Handa et al., 2015). The role of oxidized lipids has also been studied in wild-type C57BL/6J and BALB/c mice following immunization with oxidized LDL-C that resulted in sub-RPE deposit accumulation with RPE lesions resembling GA (Hollyfield et al., 2008). A transgenic mouse model (*Fat-1*) has been developed for overexpressing n-3 fatty acid desaturase that converts n-6 to n-3 FAs (Kang, 2007). Although this mouse model does not represent the human-like lipid profile (Kim et al., 2012) (Table 3), it is a good model for understanding the molecular mechanism behind the role omega-3 FA in lipid metabolism. It has been shown, that the increased level of omega-3 in these animals reduced the hypoxic stimulus for neovascularisation by controlling vessel loss (Connor et al., 2007). Zebrafish had also been used as model system for dyslipidemia (Landgraf et al., 2017; Schlegel, 2016; Schlegel and Gut, 2015). Zebrafish carry the ortholog of the human *CETP* gene and have similar lipoprotein composition to humans (Schlegel, 2016). They are also susceptible to high-fat diet-induced obesity, hyperglycemia and dyslipidemia. Zebrafish has functional LDL-R and atherosclerotic plaque-like deposits are formed when the animals are raised on high fat diet (Schlegel, 2016). In light-induced retinopathy there was enhanced retinal apoptosis (Ashikawa et al., 2017). Therefore, zebrafish might become a highly suitable model to study human-like lipid metabolism.

6.3. Cellular models for lipid metabolism

Chronic energy enriched diet combined with genetic predisposition can lead to an overload of fatty acids, generating lipid-intermediates, such as DAG, ceramides, acyl carnitines and long-chain fatty acyl-CoA, which leads to impaired cellular signaling, mitochondrial dysfunction, endoplasmic reticulum stress, and cell death (Holland et al., 2011; Jaishy and Abel, 2016). Therefore, it is imperative to study the potential effects of lipids on cells and culture cells are ideal model for this.

Wild-type or genetically modified fibroblasts and Chinese Hamster Ovary cells have turned out to be useful for studying alterations in cellular cholesterol homeostasis and led to the discovery of intracellular molecular pathways involved in lipid metabolism (Goldstein et al., 2002). Wymann and Schneiter published a comprehensive review about cellular lipid signaling in disease, which can be a good starting point for studying relevant signaling pathways in AMD (Wymann and Schneiter, 2008). In dyslipidemia, adipocytes, monocyte/macrophages and cardiomyocytes are also models for studying lipid metabolism (Leiva et al., 2017). To study lipid signaling cells can be starved of nutrients (Walch et al., 2015). Upon starvation, lipids are mobilized and broken down to fatty acids, which then serve as energy source (Finn and Dice, 2006). Culturing cells in Hanks' Balanced Salt solution or in 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid buffer led to the discovery of inter-organelle lipid flux, involving the process of lipolysis, autophagy and mitochondrial beta oxidation of fatty acids (Rambold et al., 2015; Settembre et al., 2013). The most commonly used lipid supplement for lipid metabolism studies in cell cultures are oleic and palmitic acids conjugated albumin (Choi et al., 2009; Da Silva et al., 2017; Lizaso et al., 2013; Mao et al., 2015; Singh et al., 2009) although other studies used different lipid supplements like oxidized LDL-C with 10% fetal bovine serum (FBS) (He et al., 2017; Li et al., 2017).

Skeletal muscles, heart and kidney epithelium have the major energy consumption from mitochondrial fatty acid β-oxidation and not from glycolysis (Houten et al., 2016). It has been shown that the same is true for RPE as well (Reyes-Reveles et al., 2017), therefore lipid availability is key to these cells. As we discussed in Section 5 the RPE has three different sources of lipids: 1) delivery of lipoproteins from the plasma; 2) phagocytosis of cholesterol-rich rod photoreceptor outer segments, 3) endogenous cholesterol synthesis. All of these sources will need to be considered for suitability of cellular models especially for AMD.

As cells in culture are generally grown in the presence of heat-inactivated FBS, they are grown in the presence of "circulating" lipids. FBS is commercially available, however, the composition of FBS is rarely analyzed. Different sera contain distinct compositions of fatty acids (Lagarde et al., 1984), and this might directly influence cell culture experiments (Marazzi et al., 2011). There are ways to deplete FBS of its lipids (Rothblat et al., 1976) and cells can be cultured in serum-free or chemically defined media (Adijanto et al., 2014; Reyes-Reveles et al., 2017; van der Valk et al., 2010) to overcome experimental variability.

In the eye 10% of the photoreceptors outer segments are shed daily. Consequently, the RPE must deal with the phagocytosis of numerous outer segment tips, their lipids, such as palmitate, arachidonic acid and DHA and protein content (Adijanto et al., 2014; Reyes-Reveles et al., 2017; Rodriguez de Turco et al., 1990; Young, 1967; Young and Bok, 1969) that can be used as an excellent energy source. Reyes-Reveles et al. supplemented primary human RPE either with palmitate or outer segments and showed that RPE cells produce ketone bodies through fatty acid beta oxidation (Reyes-Reveles et al., 2017). They suggested that beta-oxidation of fatty acids and ketogenesis are key elements for RPE lipid metabolism and in prevention of lipid overload. Interestingly, they did not observe any ketone body increase upon oxidized outer segment supplementation (Reyes-Reveles et al., 2017). This might need to be considered in future cell biology experiments for AMD.

To study endogenous cholesterol synthesis cell culture model are needed. Works on freshly isolated primary human RPE cell are the most promising cell model systems studying RPE biology in AMD. In a recently publication RPE cells were isolated by magnetic cell sorting from the macular region of genotyped AMD donors and controls and the cells were characterized in a variety of ways (Golestaneh et al., 2017). This study showed that cells from AMD patients are different in numerous ways from those in control. Altered autophagy, which play a pivotal role in maintaining cellular lipid homeostasis (Jaishy and Abel, 2016), was signifficantly altered, which was accompanied by mitochondrial dysfunction and the accumulation of intracellular lipid droplets (Golestaneh et al., 2017). Similar results were reported by using induced pluripotent stem cells (iPSC)-derived RPE cells from AMD donors (Golestaneh et al., 2016). Although questions remain on whether iPSCs retain the epigenetic memory of their tissue of origin, and spontaneous genetic mutations may be introduced through the experimental process (Chakradhar, 2016; Hu et al., 2010; Kim et al., 2010; Polo et al., 2010), iPSC cells can produce extracellular lipid and lipoprotein deposits (Galloway et al., 2017). However, isolation of primary RPE cell without passage from AMD donors is difficult while iPSC-derived RPE generation is time-consuming and expensive. Passaged primary RPE cells can provide a reliable alternative for cell biology studies. Primary human fetal RPE cells differentiated into mature RPE cells showing all the characteristic features of native RPE (Johnson et al., 2011; Pilgrim et al., 2017). These cells can secrete and deposit APOE in the sub-RPE space and, like primary or iPSC derived RPE, can serve as model for lipid metabolism despite the absence of photoreceptor outer segments in the apical culture medium. Therefore, cellular synthesis and lipids from the culture medium can provide a permissive environment for sub-RPE lipid deposition.

Isolation of primary cells from animals are often used in experiments, though they suffer the same problem as their host, that is the lipid metabolism is different from human even after genetic modifications (see section 6.1.). Nevertheless, a recent study using pig primary RPE cells could recapitulate many aspects of sub-RPE deposits formation despite the lack of CETP in pigs (Pilgrim et al., 2017) including lipid, APOE and hydroxyapatite accumulation.

Despite the successes with primary cells, one of the most widely used RPE cell models is ARPE-19, a human RPE cell line established by Dunn et al. (1996). This immortalized cell line can differentiate into primary RPE-like cells (Ahmado et al., 2011; Samuel et al., 2017) though there are problems with these cells, such as low expression of tight junction, low transpithelial resistance (Luo et al., 2006). When ARPE-19 cells were cultured in high glucose and serum-free media the cells accumulated intracellular cholesterol, synthesized and transported fatty acids and following LDL-C supplementation they abolished gene expressions for lipid synthesis pathways, while lipid transporter gene expression remained elevated (Mishra et al., 2016). In other studies, ARPE-19 cells were treated with carotenoid-enriched human serum or isolated human serum lipoproteins in combination with carotenoids in serum-free media (Thomas and Harrison, 2016). Recently a novel supressive role for apoliporotein M in angiogenic and inflammatory responses had been postulated in ARPE-19 cells. This could be interesting as another treatment option for neovascular AMD, beyond anti-VEGF therapy (Terao et al., 2017).

There are attempts to use complex cellular co-culture systems to study AMD associated lipid metabolisms in which RPE and endothelial cells are sandwiched together (Choudhary et al., 2016) or retinal explants are cultured on pre-seeded RPE cells (Reyes-Reveles et al., 2017; Valdes et al., 2016).

In addition, photoreceptor cell models are also available. Rotstein and Politi developed a primary rat photoreceptor cell culture model and extensively studied the protective effect of DHA on cell survival (German et al., 2006).

Studies with detailed analysis of lipid biosynthesis are just emerging (Mishra et al., 2016; Wang et al., 2016a). Similar, or even more comprehensive studies will be needed to gain the necessary depth of information to understand how *de novo* lipid synthesis may contribute to AMD.

6.4. Imaging of lipids in animal and human eyes

Histochemical detection of lipids in AMD was shown first using Sudan-black B staining (Streeten, 1961; Wolter and Falls, 1962). Using bromine-acetone immersion followed by Sudan black B demonstrated also the presence of phospholipids that withstand acetone extraction (High, 1984). Oil red O staining demonstrated the presence and distribution of neutral fats, especially esters of saturated and unsaturated fatty acids (Pauleikhoff et al., 1990). Exposure to a general lipid solvent (1% HCl in chloroform and methanol 2:1), proved the specificity of Oil Red O to lipids. Since these original colorimetric studies several fluorescent based probes had been developed for different lipid probes (Johnson, 2010). Filipin staining is probably the most widely used fluorescent lipid dye that can be used to distinguish cholesterol and its ester form (Curcio et al., 2001). To avoid potential processing artefacts tissues can be viewed by hot stage polarization microscopy to identify the presence and distribution of different lipid subtypes in histologic sections based on morphology and melting temperatures of liquid crystals (Haimovici et al., 2001).

With advancement of microscopic technologies lipid particles were identified on electron microscopic images as electron lucent particles in human eyes (Nakaizumi et al., 1964) as well as animal models (Sallo et al., 2009). The cause of the electron lucency was due to removal of lipids through processing of samples. This could be avoided by the introduction of tissue postfixation with osmium-tannic acid-paraphenylenediamine (Curcio et al., 2001) that preserves neutral lipids (Guyton and Klemp, 1988). The best way to retain lipids for electron microscopy, however, is avoiding chemical processing. Quick-freeze/deep-etched samples allowed significant improvement in the characterization of the lipid particles in the different layers of Bruch's membrane and drusen (Huang et al., 2007, 2008).

However, the most comprehensive molecular detection methodologies are imaging spectrometry. While resolution does not compete with the fluorescence labeling methodologies, identification of specific species are possible with matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) imaging (Anderson et al., 2014) or secondary ion mass spectroscopy (Thompson et al., 2015). In addition, several lipid-related changes were reported in the Bruch's membrane using Raman spectroscopic imaging that has been used to visualize non-oxidized monounsaturated fatty acid-based lipids, cholesterol or oxidized polyunsaturated fatty acid-based in flat mount Bruch's membrane (Beattie et al., 2010).

Increasing specificity of probes and resolution of molecular analytic methods should be able to identify the exact position and movement of lipid molecules in and around cells.

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7. Lipid-related treatment options for AMD

The results from studies on dietary (section 2) and circulating (section 3) lipids, together with results from genetic and Mendelian randomization studies (section 4), support a role for both circulating lipoproteins as well as local lipid trafficking in the retina in AMD pathogenesis. An important next step is to determine whether treatments should target the systemic lipoproteins metabolism, the local lipid metabolism in the retina, or both. In this section, we review the potential of drugs targeting the lipid metabolism, either systemically or locally, as possible future treatments for AMD.

7.1. Statins as a treatment option for AMD

The association of circulating lipoproteins in AMD (section 3) led to the postulation that statins, which are known to be beneficial in atherosclerosis and hyperlipidemia, may exert protective effects in AMD by different mechanisms (Gehlbach et al., 2016). In this section, we summarize the potential pharmacological effects of statins on AMD and the results reported in the literature on the association between statins and AMD.

In AMD, an accumulation and retention of APOB and cholesterol have been reported (Curcio et al., 2011). Lipid components of drusen come from local tissues, (retina and RPE secreting APOB and APOE, which contain lipoproteins) (Wang et al., 2009) and from the circulation (Curcio et al., 2011; Wu et al., 2010). It is known that both AMD and atherosclerotic CAD involve lipoprotein retention. Mechanistically, statins suppress cholesterol synthesis by inhibiting HMGR, and thus may reduce local and circulating lipid production. In addition, statin reduce cholesterol synthesis and inhibit CE-rich APOB100 lipoprotein secretion in cultured human RPE cells via modulation of RPE cholesterol levels (Wu et al., 2010). Thus, statins may reduce local accumulation and retention of APOB and cholesterol.

The RPE is susceptible to chronic oxidative stress, which may play a role in AMD pathogenesis (Klein et al., 2014b). It has been suggested that oxidized lipids found in Bruch's membrane and the RPE may be the first process leading to inflammation in AMD (Schutt et al., 2003; Spaide et al., 1999). Accordingly, the use of statin may reduce oxidative stress by protecting the outer retina, Bruch's membrane, and choroid from oxidative damage and consequently decrease the risk of triggering an inflammatory response. Macrophages play an important role in impaired cholesterol efflux and reverse cholesterol transport, which can lead to tissue inflammation and neovascularisation, suggesting a crucial role for macrophage in AMD (Sene and Apte, 2014). Mechanistically, statins, by their lipid-lowering effect may reverse these aging changes in macrophages and consequently reduce progression to neovascularisation. In addition, besides their effect in lowering LDL-cholesterol, statins also lower plasma concentrations of C-reactive protein (Jialal et al., 2001), which have been associated with a higher risk of AMD incidence (Mitta et al., 2013), although the exact physiopathological mechanism remains to be clarified (Chirco and Potempa, 2018).

Higher intraocular levels of VEGF have a main role in the development of neovascularisation in AMD. It has been reported that statins reduce plasma levels of VEGF and down-regulate several transcription factors involved in VEGF expression (Dichtl et al., 2003). Thus, statin use may reduce the incidence and progression to neovascularisation through regulation of VEGF levels (Dichtl et al., 2003).

Despite the evidence of these mechanistic effects of statins, the association between the use of cholesterol-lowering medications and AMD has been inconsistent. Several studies suggested a protective effect of statin use on AMD (Drobek-Slowik et al., 2008; Friedman et al., 2005; Hall and Martyn, 2002; McCarty et al., 2001; McGwin et al., 2003, 2005; Tan et al., 2007; Vavvas et al., 2016; Wilson et al., 2004) while others reported no significant association (Cougnard-Gregoire et al., 2014; Delcourt et al., 2001; Hogg et al., 2008; Kaiserman et al., 2009; Klein et al., 2001b, 2003, 2007; Maguire et al., 2009; McGwin et al., 2006; Shalev et al., 2011; Smeeth et al., 2005; van Leeuwen et al., 2003) or even showed adverse effects (Etminan et al., 2008; VanderBeek et al., 2013). However, none of the studies examined simultaneously the effective dose, treatment duration and potency of statin therapy on AMD. Apart from the few randomized controlled trials (RCTs) (Guymer et al., 2008, 2013; Vavvas et al., 2016), most of these studies were observational with methodological limitations, bias and confounding factors. The most promising results come from a recent multicenter interventional prospective pilot trial, treatment of at least one year with high dose atorvastatin showed regression of drusen deposits and improvements of visual acuity in 10 out of 23 patients with high-risk features for progression to AMD (Vavvas et al., 2016). Despite the encouraging positive results, this trial was limited by the small sample size and lack of comparison with a placebo control group. Therefore, well-designed, large prospective cohorts and RCTs are needed to determine the potential role of statin in preventing or delaying the onset or progression of AMD.

Fenofibrate is often used along with other cholesterol drugs, such as statins (Jones et al., 2010). It is regarded as broad-spectrum lipid lowering drugs that decreases triglyceride levels, reduces low density lipoprotein (LDL) cholesterol levels and is involved in raising high density lipoprotein (HDL) cholesterol (Packard, 1998; Pahan, 2006). Fenofibrate can inhibit fatty-acid peroxygenase activity and activate peroxisome proliferator-activated receptor alpha (PPARalfa) and through which it inhibits neovascularistaion in the retina and augments the protective effects of omega-3 LC-PUFAs on angiogenesis (Gong et al., 2016; Qiu et al., 2017).

7.2. Targeting HDL metabolism as a treatment option for AMD

The association of genetic variants in genes involved in HDL-C metabolism such as *CETP, LIPC* and *ABCA1* (section 4) suggest the possibility that pharmacologic agents targeting HDL-C could be a new therapeutic strategy to treat AMD. However, several questions need to be answered before development programs can be initiated to target HDL-C for AMD treatment. The first question is whether the pharmacologic agent should increase or decrease HDL-C. The two recent Mendelian Randomization studies (Burgess and Davey Smith, 2017; Fan et al., 2017) have found contradictory association for variants in *CETP* and *LIPC*. As described in section 4.4, a *CETP* variant associated with increased HDL-C in circulation and two *LIPC* variants associated with decreased HDL-C are associated with increased AMD risk. One possible explanation for this discordance is that the HDL-C generated by the *CETP* and *LIPC* variants has different composition and properties (section 3.2.). Alternatively, it is possible, that local HDL-C metabolism and not systemic HDL-C level is the underlying mechanism for the genetic association (section 4.4.). The question, whether local or systemic HDL-C or both are involved in AMD pathogenesis is important to address before developing pharmacological intervention. Treatment to modify circulating HDL-C can be achieved with compounds administered orally or by infusion, while modifying the HDL-C metabolism locally in the retina may require targeted delivery.

Another important question to answer is at what stage of the disease HDL-C metabolism plays an important role. Therapies that slow or prevent the progression of intermediate AMD and conversion to the advanced forms of AMD are likely to require an oral administration, which are less invasive than intravitreal injections, for instance. Oral treatments could be also an option to treat the advanced forms of AMD, but intravitreal injection might be a more effective.

Among the genes associated with AMD risk that are involved in HDL-C metabolism the best target is *CETP*. Several CETP inhibitors have been developed for treatment of cardiovascular disease and four of these drugs tested in large outcome trials (Tall and Rader, 2017). It has been clearly demonstrated that all CETP inhibitors increase HDL-C in circulation, some of them like Evacetrapib and Anacetrapib by as much as 100% (Group et al., 2017; Lincoff et al., 2017). However, considering

that *CETP* variants associated with higher HDL-C in the circulation are associated with higher AMD risk (section 4), CETP inhibitors, which would lead to higher circulating HDL-C, do not seem a reasonable strategy to treat AMD. Since the development of all CETP inhibitors as treatment of cardiovascular disease have been abandoned due to lack or low efficacy, the assessment of association of CETP inhibition in AMD is unlikely to be possible or desirable.

To date no pharmacological agents that inhibits LIPC or that increases CETP expression or activity have been developed for the clinic. Agonists of the Liver X Receptor increase the expression of ABCA1, but also have presented some undesirable side effects. Therefore, the development of therapies targeting HDL-C metabolism for treatment of AMD has still a long way to go. Modulation of HDL metabolism for AMD, however, should consider that it does not increase the risk of cardiovascular disease, where HDL plays a protective role.

7.3. APOA1 mimetic peptide as a potential novel therapy for AMD

A recent study evaluated the potential of APOA1 mimetic peptide 4F as a potential novel local therapy for AMD (Rudolf et al., 2018). APOA1 mimetic peptide 4F is a small synthetic peptide that emulates the anti-atherogenic properties of APOA1, the main protein of plasma HDL. 4F binds oxidized phospholipids and fatty acid hydroperoxides in cellular membranes with high affinity, and has been shown to reduce atherosclerotic lesions in animal models (Navab et al., 2006a, 2006b; Reddy et al., 2014). In phase II clinical trials for cardiovascular disease, 4F improved the HDL anti-inflammatory index in one study but did not improve HDL functional biomarkers in another study, and was well tolerated in both studies (Bloedon et al., 2008; Watson et al., 2011). Intravitreal injection of 4F in *Apoe*^{null} mice showed a dose-dependent reduction of esterified cholesterol in Bruch's membrane, and restoration of the ultrastructure of Bruch's membrane. The APOA1 mimetic peptide 4F may thus represent a new approach to treat the AMD process locally by removing lipid deposits from Bruch's membrane (Rudolf et al., 2018).

In addition to these, zinc supplementation, used in AREDs (Age-Related Eye Disease Study 2 Research Group, 2013; Age-Related Eye Disease Study Research Group, 2001), could affect lipid biosynthesis. It has been shown that zinc deficiency can affect levels and/or compositions of cholesterols, phospholipids, triglycerides, fatty acids and lipoproteins (Bettger et al., 1979; Cunnane, 1988; Cunnane et al., 1981). Zinc can serve as cofactor of various biosynthetic enzymes, mainly investigated in adipose tissue and liver (Eder and Kirchgessner, 1995; Justus and Weigand, 2014; Tepaamorndech et al., 2016).

8. Future directions & conclusions

From a physiological perspective, it is unlikely that the biological systems within the human body would operate independently from each other in health or in diseases like AMD. Therefore, integration of biological systems into a coherent and all-encompassing biological understanding is needed to identify the precipitating event(s) that lead to the development and progression of AMD. The possibility of an integrative approach is now at our doorstep with the deeper and better understanding of genetic, cellular and molecular processes. Significant progress has been made recently to understand the association between lipids and AMD but we still need to clarify whether the lipids that enter the body through the diet and/or the lipids produced locally by specific cells or tissues are the target for intervention.

Epidemiological studies identified a clear relationship between dietary fatty acid intake and AMD. However, despite the protective effect of dietary omega-3 PUFAs (omega-3 LC-PUFAs like EPA + DHA), trials with supplemented PUFAs showed mixed results. We do not yet know which population could benefit most from supplementation and which supplementation might be optimal in one country or ethnic population compared to another. Lipids are consumed in combination with other nutrients in our diet and these may directly affect lipid metabolism. In support of this, recent studies have shown that the Mediterranean-type diet, a diet rich in PUFAs and antioxidants, may help to reduce the onset and progression of AMD probably more effectively than those of supplemented lipids (Hogg et al., 2017; Mares et al., 2011; Merle et al., 2015). Twenty percent of dry weight of the retina is composed of lipids (Whitehead et al., 2006), with at least fifty percent of these being unsaturated (Preedy, 2014). Therefore, lipid oxidation is expected to play a role in pathological processes in AMD. This was proven when the association of advanced lipid peroxidation end-products to AMD was presented (Crabb et al., 2002; Gu et al., 2003; Shaw et al., 2012). Based on these it was suggested that endogenous and dietary antioxidants might be crucial for the defense against damaging free radicals (Age-Related Eye Disease Study 2 Research Group, 2013; Age-Related Eye Disease Study Research Group, 2001). Antioxidants counteract lipid peroxidation either by hindering or scavenging reactive oxygen species or by stalling radical chain propagation (Laguerre et al., 2007). Dietary nutrient intake showed significant improvement on the defence against AMD (Preedy, 2014). In the future it will be important to consider the multidimensional nature of the diet and the patterns of nutrition locally and globally for AMD. It is likely that further observational studies and clinical trials are needed to better understand and characterize the role of nutrition, particularly PUFAs role in AMD prevention.

It has been suggested that circulating biomarkers for PUFAs will help identify those individuals who may benefit most from nutritional intervention. Such biomarkers could be used to monitor the efficacy of nutritional or pharmacological interventions in restoring adequate nutritional status. However, it is not clear whether the intake of dietary lipids and circulating lipoproteins levels are in direct association with the risk for developing AMD. An association between circulating HDL-C and AMD has been described, but it is difficult to unequivocally infer what the role of serum lipid particles is in AMD. Genetic studies of AMD have reported associations with variants in several genes involved in lipid metabolism. Mendelian randomization studies have pointed towards a causal role of long-term elevated HDL-C levels in increasing AMD risk. However, these studies have shown that *CETP* and *LIPC* variants associated with higher HDL have opposite effects on AMD. This may rather suggest that these variants have a local effect on the lipid metabolism in the retina. This local effect on retina lipid metabolism is also suggested by the very high cholesterol load in photoreceptors and the expression of several of the AMD-associated genes (*ABCA1*, *CETP*, *APOE*) in the retina. Indeed, these genes encode components of the local lipid trafficking machinery in the retina.

As the effects of circulating lipoproteins levels on retinal lipid accumulation in human is not well understood, several model systems have been used to understand the changes in circulating lipoproteins metabolism on cells and tissues. Given the variability of animal plasma lipoproteins profiles and their differences from the human profiles makes translation of results to human difficult. Development of human-like dyslipidemia in animal models could help in this, but extensive characterizations will be needed before translation to human can be done. Human cellular models have the potential to provide vital information as comprehensive omics approaches, like the combination of proteomics, lipidomics, metabolomics and transcriptomics, on these cells would certainly contribute to a fuller understanding for the association of local lipid changes to AMD. Single cells types are, however, studied usually in isolation which will limit their value for the whole of the retina. Organoids are emerging as potential future model system, but they might represent the same challenges as any other model systems.

Collective investigations applying metabolomics and, in particular, lipidomics would help to understand the systemic effect of genetic variants as has been shown for other complex diseases (Suhre et al., 2011). Moreover, the utilization of lipidomics will have the potential to elucidate the intricate role of the RPE to control lipid homeostasis of the

retina in cell models. In addition, as this analytical technique can be used in high throughput due to latest developments in mass spectrometric technology (Bowden et al., 2017; Weir et al., 2013), one could even think of routine standardized analysis of dietary components and supplements to better understand their role in ocular health. Lipidomics offers also the opportunity to identify new markers for progression or prognosis, even unexpected ones, e.g. of microbiomic origin, as has recently shown for other neurodegenerative diseases (Sampson et al., 2016). It is known that the RPE controls the uptake of lipoproteins into the retina. This is of major importance as the photoreceptors require a large quantity of cholesterol each day to replace the shed membrane disks. While both the RPE and photoreceptors are capable of synthesizing their own cholesterol via the tightly regulated mevalonate pathway, the retina produces only 72% of the cholesterol it needs while the remaining lipids are acquired from the circulation. As the RPE contributes to the retina-blood barrier, it must control the balance of lipids. Hence the RPE controls lipid homeostasis by the creation and efflux of lipoprotein particles. What remains unknown is to what extent the systemic circulation influences the lipid homeostasis in the retina. For example, one of the first clinical signs of AMD is poor night vision. With fatty acids, especially DHA, interrupting the shuttling of the vitamin A cycle in the interphotoreceptor matirx by preferentially binding with IRBP, this could be an interesting place to explore in future work.

In addition to the lipoprotein balance, the composition of lipoproteins might be also of high importance as this can affect their functional role. It might also be important to consider the dynamic nature and modifiable character of the protein content of lipoprotein particles, as has been reported in cardiovascular disease and rheumatoid arthritis (Green et al., 2008; Watanabe et al., 2012). Lipoprotein compositions might be changed from being harmful, thereby changing the functionality of the lipoprotein complex. This might be an exciting novel approach for therapy in the AMD. Insight into whether the compositions of lipoprotein particles can be modified in AMD by nutritional or pharmacological means could open new therapeutic intervention possibilities. This also implies that determining the exact composition of the HDL-C particle could reveal more precise biomarker for AMD.

Recent evidence from genetic, functional and physiological studies suggest the potential interaction between the complement system and lipoprotein homeostasis, but the exact mechanisms need to be fully elucidated. It will be interesting to explore whether there is a direct association between complement components and lipoprotein particles, or whether the complement system affects the composition and physiological function of lipoprotein particles in AMD, opening further therapeutic intervention possibilities.

Targeting circulating levels of HDL-C alone in AMD, without the understanding whether this systemic change in levels contributes to the pathology of the disease, might be premature. This seems to be supported by the available observational, animal studies and RCTs with statins. RCTs with a valid measure of treatment effect (such as vision related outcome), long duration of treatment, long follow-up, larger population and appropriate placebo control group will be needed to clarify this issue.

Competing financial interest of the authors:

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.preteyeres.2018.04.006.

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