## Associations of Alzheimer's disease with macular degeneration

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## 1. ABSTRACT

There is growing evidence of epidemiological, genetic, molecular and clinical links between Alzheimer's disease (AD) and age-related macular degeneration (AMD). Major interest in the relationship between AD and AMD has derived from the evidence that beta-amyloid, the main component of senile plaques, the hallmark of AD, is also an important component of drusen, the hallmark of AMD. This finding has a great potential in the present era of anti-amyloid agents for the treatment of AD. The connection between AD and AMD is also supported by the evidence that the two diseases share other pathophysiological factors, such as oxidative stress and neuroinflammation. Accordingly, a few clinical trials have evaluated the efficacy of antioxidants on visual and cognitive performance in patients presenting both disorders. In this review, we summarize the pathophysiological and clinical evidence of the relationship between these two age-related disorders. Considering the increasing prevalence of both conditions along with the aging of the population, further investigations of this important issue are highly needed.

## 2. INTRODUCTION

Recently, many efforts have been done to investigate the possible link between two common age-related disorders, i.e. Alzheimer's disease (AD) and age related macular degeneration (AMD), the leading cause of blindness in the elderly population (1). AD is the most common neurodegenerative dementia, representing over 50 percent of all causes of dementia (2).

Beta-amyloid (A beta), the main component of amyloid plaques in Alzheimer's disease, is also located in drusen, that are the hallmarks of AMD, *for review see* (3,4). Drusen deposits are focal deposition of acellular debris between the retinal pigment epithelium (RPE) and Bruch's membrane. They are common findings already at the early stages of the disease (5).

These two diseases share many pathogenic mechanisms, such as neuroinflammation and oxidative stress, *for review see* (6), and several risk factors such as age, obesity, atherosclerosis and hypertension (7), *for review see* (3). Hence, the similarity between these two degenerative diseases is sufficiently evident to allow some authors to speculate that AMD could be "*Alzheimer disease in the eye*" (8).

## 3. ABOUT AMD

Based on the histopathological aspects and the clinical progression, AMD was categorized in different subtypes by the Age-Related Eye Disease Study (AREDS) severity scale grading system (9). According to this classification, early AMD is characterized by few
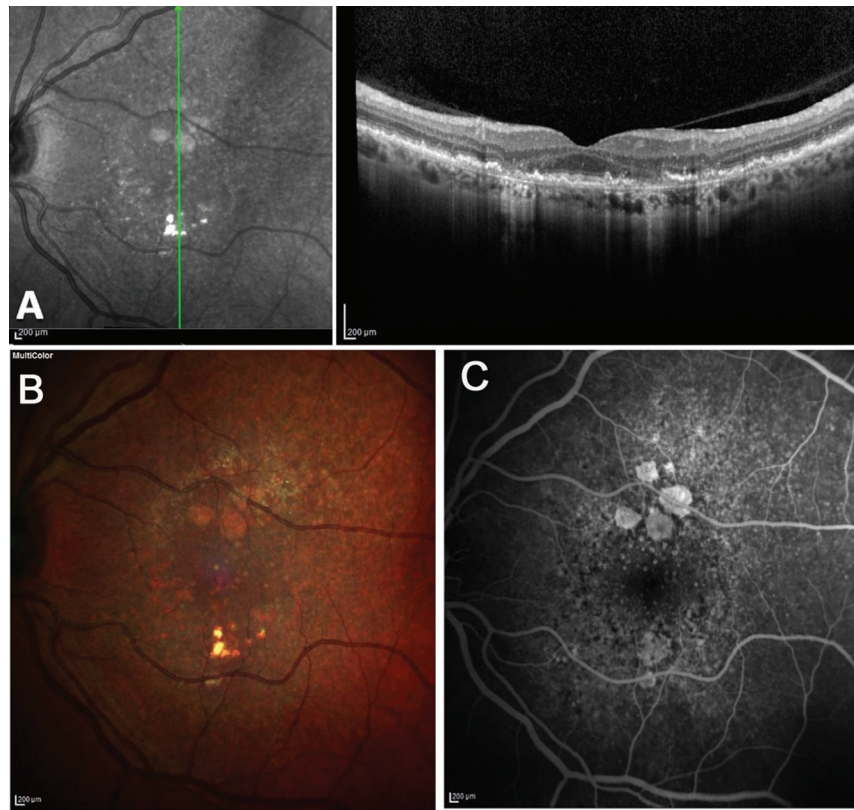
**Figure 1.** Normal eye imaging. Horizontal SD-OCT scan (A, right) with the plane of the section demonstrated in green in a OCT fundus image (A, left). MultiColor™ – Scanning Laser Imaging (B). FAG imaging (C).
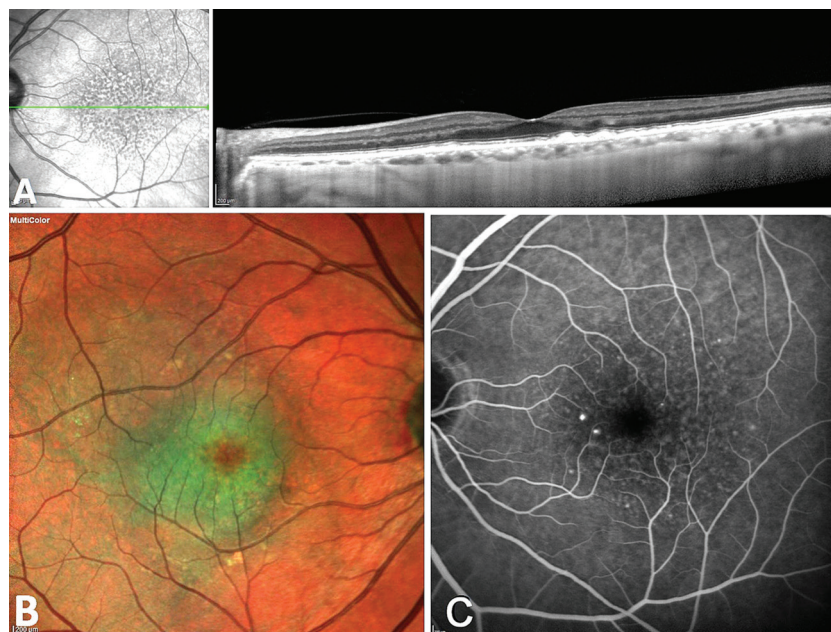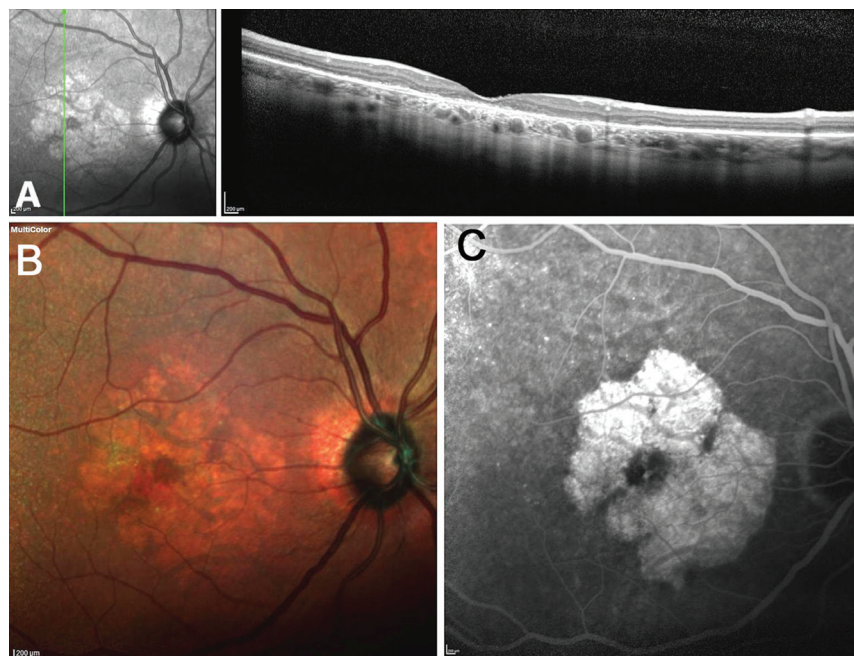


**Figure 2.** Early AMD. Horizontal SD-OCT scan (A, right) with the plane of the section demonstrated in green in a OCT fundus image (A, left). MultiColor™ – Scanning Laser Imaging (B). FAG imaging (C).

small (smaller than 63 um) along with numerous medium-size drusen (greater than 63 but smaller or equivalent to 125 um) see in Figure 1 a normal eye and in Figure 2 an eye affected by early AMD. It can progress in severity (see Figure 3) to one of the two advanced forms of AMD: dry (i.e. non neovascular) AMD characterized by the presence of drusen and atrophy of the RPE and choroid (see Figure 4); or wet AMD (neovascular) (1,10), defined by newly formed vessel (choroidal neovascular membrane (CNV)) and RPE detachment (see Figure 5) (10). Wet AMD is thought to exist in two subtypes, Classical Choroidal Neovascularization (CNV) and Polypoidal Choroid Vasculopathy (PCV), although many authors consider PCV as a distinct clinical entity (10,11).

**Figure 3.** Intermediate AMD. Vertical SD-OCT scan (A, right) with the plane of the section demonstrated in green in a OCT fundus image (A, left). MultiColor™ – Scanning Laser Imaging (B). FAG imaging (C).



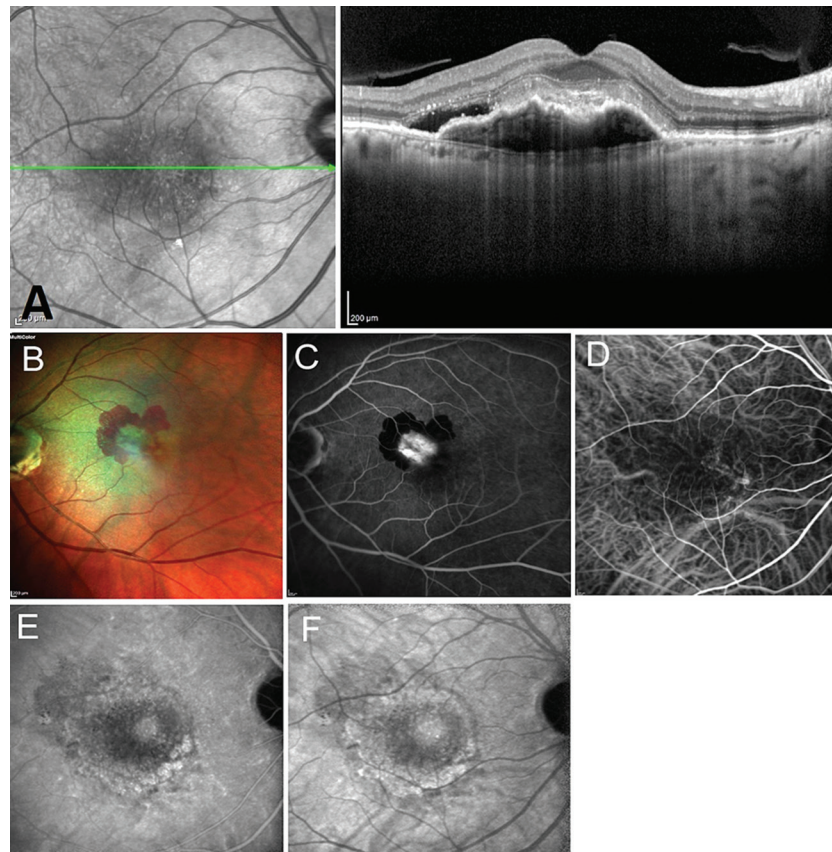**Figure 4.** Advanced AMD: dry form. Vertical SD-OCT scan (A, right) with the plane of the section demonstrated in green in a OCT fundus image (A, left). MultiColor™ – Scanning Laser Imaging (B). FAG imaging (C).

**Figure 5.** Advanced AMD: wet form. Horizontal SD-OCT scan (A, right) with the plane of the section demonstrated in green in a OCT fundus image (A, left). MultiColor™ – Scanning Laser Imaging (B). FAG imaging. (C). ICG angiography: early (D), intermediated (E) and late (F) scans.

## 4. EPIDEMIOLOGICAL ASPECTS OF AD AND AMD

AD is the most prevalent cause of dementia and could account up to 70 percent of cases of dementia (12). The burden of this disease on worldwide healthcare can be easily understood by looking at its general prevalence, which is estimated to count 46 millions of cases worldwide (12), with the number of AD patients expected to triple in 2050 (13), reaching 131 million of cases (14). Moreover, it is possible to speculate that the real prevalence could be higher due to the underdiagnosis of AD, especially among the oldest old (15,16). To this regard, there is evidence of a possible overlap between cerebrovascular dementia and AD dementia pathology, thus cases previously classified as vascular dementia could have been joined today in the AD category (17). Anyway, it's worth to mention that a definition of AD can differ when using clinical criteria of dementia not otherwise explained, imaging methods or biomarkers essay, leading thus to different estimation of AD prevalence (18). The prevalence of AD is differing among countries and shows to be higher in western countries as US and Western Europe. In these countries, there is evidence of a cohort effect with later-born individuals showing a lower risk than the ones born in the last century (12).

AMD, likewise, has been reported to be the leading cause of blindness and severely impaired vision (visual acuity < 6/18) in non-Hispanic white people by several studies (19-23). The pooled prevalence (any form and stage of AMD) of AMD worldwide was found to be around 9 percent, with a higher prevalence in Europeans (12 percent) than Asians (7.4. percent) or Africans (7.5. percent), in a systematic review of previous works (24). The number of people affected is expected to increase in all population groups in the next decades, with overall 196 million of people with the disease in 2020 and 280 million in 2040 (24). Although the pooled prevalence of any type of AMD has proven to be high, a great part of this percentage is attributable to early and intermediate AMD (8.0.1. percent). A recent systematic review has reported that prevalence of advanced AMD is definitely lower (0.3.7. percent) (24). It should be noted that the majority of epidemiological studies on AMD has excluded early AMD (23,25) which covers 85-90 percent of the cases. For a better understanding, the current classification of AMD subtypes and severity has been

**Table 1.** Classification of AMD subtypes

| Condition | Drusen size | Neoangiogenesis | Epithelial degeneration | References |
|---|---|---|---|---|
| Early AMD | Medium drusen ( larger than 63 but equivalent to or smaller than 125 um) | Absent | Absent any pigmentary abnormality | (10,97) |
| Intermediate AMD | Large drusen (larger than 125 um) | Absent | Pigmentary abnormalities alone or associated with large drusen | (10,97) |
| Advanced AMD | Whichever | Defined by the presence of Geographic atrophy or any form of neoangiogenesis | | (97) |
| Dry AMD | | Absent | Geographic atrophy | (97) |
| Wet AMD | | Present | RPE detachment | (10,97) |
| Classical CNV | | Choroidal neovascularization usually located between the neurosensory retina and the RPE | RPE detachment | (10) |
| PCV (Considered by many authors as a distinct entity) | | Branching vascular network with polypoidal lesions under the retinal pigment | Serous or hemorrhagic detachments of the RPE | (98,99) |

**Table 2.** Overview of risk factors for AMD and AD

| Risk factors | AD | AMD | References |
|---|---|---|---|
| Aging | + + + | + ++ | (27) (24,28) |
| Genetic | | | |
| CST3 | + +[1] | + +[1] | (33,40) (40) |
| TNF | + | + | (33) |
| APOE epsilon-4 | ++ | --- | (33) (100) |
| APOE epsilon-2 | --- | ++ | (32,33) (101) |
| CFH and ARMS/ HTRA1 | + | +++ | (36) (31,34,35,37) |
| Smoking | ? | +++ | (9,35,42–44) |
| High BMI | + | + | (12) (102) (103) |
| Diabetes mellitus | ++ | + | (49) (51) |
| Blood pressure | ++ | + | (12) (102) (104) (25) |
| Hyperlipemia | ++ | ? | (105) (106) |
| Diet rich in saturated lipids | + | + | (12) (107) (25,88) |
| Low vitamin D serum levels | + | + | (108) (109) |

summarized in Table 1. In the context of exudative AMD, a different prevalence between Europeans and Asians of two different patterns of neovascularization - CNV and PCV - has been observed. Population studies have shown the latter to be more prevalent in Asian populations while the former in the western populations (26).

## 4.1. Risk factors, protective agents and associated conditions

Risk factors, protective agents and associated conditions of AD and AMD are reported respectively in Tables 2, 3 and 4.

Age is the strongest risk factor for AD. The incidence of AD increases yearly by 0.5. percent in the age group 65-70, and by 6-8 percent in subjects aged 85 or older (27). AMD as well was found to be a condition strongly related to aging. Two meta-analyses have investigated the epidemiology of AMD, gathering data respectively from 39 (24) and 30 studies (28). The first one found early AMD prevalence increasing with age (24) while the second one has detected an odds ratio (OR) for late AMD increasing 4.2 points (3.8.6. – 4.6.3.) every decade (28). In Wong's meta-analysis, there were no consistent differences between sexes in terms of AMD prevalence (24). When we look at AD global prevalence, it is well documented that it is more frequent among women than among men (with over 60 percent of persons with AD being female) (29), but this has been generally attributed to the women's greater life expectancy. Thus, after adjusting for age, AD presents a similar scenario to the AMD's one (18,29).

Genetics has demonstrated to play a main role in the development of AD and AMD, with a heritable component ranging between 45 percent and 70 percent (30,31) for AMD and even more for AD (about 60–80 percent) (12). Rare mutations in three genes have been firmly implicated in familiar early-onset disease: *APP*, *PSEN1*, and *PSEN2* (27). These genes show high penetrance (greater than 85 percent) and are inherited in an autosomal dominant fashion (12). APOE is the strongest common genetic variant for late-onset AD. Among its known polymorphisms, epsilon-3 is considered a neutral allele, epsilon-4 the high-risk allele, and epsilon-2 a protective allele. The epsilon-4 allele influences age at onset in a dose-dependent manner. APOE gene has been also linked by a set of studies with AMD. Surprisingly, epsilon-2 and epsilon-4 alleles are, in contrast to AD, respectively risk and protective factor

**Table 3.** Overview of protective factors for AMD and AD

| Protective factors | AD | AMD | References |
|---|---|---|---|
| Vitamin A, C, E, carotenoids | ++ | + + | (45) (12) (102) (25) (110) |
| Intake of folates | ++ | ? | (45) |
| Estrogen Exposition | + | ? | (45) |
| Homocysteine, Folate, B12 | ++ | + | (45) (102) |
| APOE epsilon-2 | ++ | -- | (33) |
| APOE epsilon-4 | -- | ++ | (33) (101) |

**Table 4.** Overview of AMD and AD associated conditions

| Associated condition | AD | AMD | References |
|---|---|---|---|
| Stroke | ++ | ++ | (111) (52) |
| Obstructive sleep apnea | ? | + | (55) |
| Thyroid dysfunction | + | + | (112) (113) |

for AMD (32). However, other studies failed to confirm this association (33). The most important genetic risk factors for AMD are *CFH* (encoding for a complement inhibitor factor) and *ARMS2/HTRA1* (encoding for a serine protease) with an OR for AMD greater than 3 in the homozygote carriers (33-35). In Woo's study, *ARMS2/HTRA1* mutation was found to be associated with the exudative (wet) pattern of AMD and with their subtypes, typical CNV and PCV. The same study has confirmed also the association of *CFH* with exudative AMD but has not identified any correlation with its subtypes (35). One study has also found a possible association between a polymorphism of CFH, strongly associated with AMD, and AD; this gene could act interacting with APOE-epsilon-4 (36). Several genetic risk scores (GRS) have been perfected to predict the likelihood of developing AMD in subjects with selected genetic alterations; in 2016, a review was performed in order to assess their accuracy (31). According to this analysis, the most accurate GRS resulted to be the one developed by Seddon (37), which included in addition to *CFH* and *ARMS2/HTRA1* also *C3*, *C2*, and *CFB* genes. This model has failed to show any influence for AD risk prediction (38). Moreover, variants in *SORL1*, which encodes a protein involved in trafficking of APP, are associated with late-onset AD (39). In 2014, a study has been conducted to directly investigate the genetic similarities between AMD and AD, based on the hypothesis of a common genetic background: ABCA7, HGS and PILRA/ZCW1P1 were identified as associated with both pathologies. Moreover, pathways analysis have shown clathrin-mediated endocytosis (CME) signaling, LXR/RXR activation and atherosclerosis signaling pathways to be linked with both AD and AMD (33). The results of this pathways analysis suggested a possible involvement of TNF gene (33). One

year later, CST3, previously confirmed by meta-analysis to be associated with AD, has been found to be associated also with exudative AMD (40). Finally, a study by Hoffman and colleagues tried to search for a possible correlation with AMD progression, defined by using drusen number and total area, and a set of selected genetic loci, but they failed to find any significant correlation (41).

Besides genetics, also environmental factors are probably implicated in the pathogenesis of both diseases. In particular, smoking for AMD has consistently been identified as a risk factor by several studies (9,35,42-44). The risk in current smokers has shown to be increased three times and smoking cessation revealed a protective effect (43). Smoking and an elevated BMI are also risk factors associated with the progression of early or intermediate AMD to advanced AMD (9,44), while their role is controversial in AD. Nonsteroidal anti-inflammatory drugs (NSAIDs) usage can act as a protective factor for AD (45). On the other hand, there is emerging, but not definite, evidence that also the use of antacids and anti-inflammatory medications could play a role in the transition between early AMD and advanced disease (9,44,46). In the AD field, also, the association between statins and antihypertensive medications use and reduction of dementia risk is strong according to a recent meta-analysis (45). With respect to AMD, even if hypertension is probably an important risk factor for this disease, until now there is no evidence that antihypertensive medications could have a positive impact on clinical outcome (47). As well, the association between cholesterol levels, statin use or alterations in the lipids pathway was found to be inconsistent in AMD (48). Arvanitakis, in 2004, found a strong association between AD risk and type II diabetes mellitus (DM) (49). Other studies have then claimed a substantial two-fold increased prevalence of AD in patients with type II DM, attributable to the amyloidogenic effect of advanced glycation end products and insulin resistance (27). Nevertheless, a recent study group which included Arvanitakis himself has found that type II DM would actually only be linked with an increased risk for cerebrovascular accidents and not with an increased risk for AD neuropathology (50). Furthermore, a meta-analysis, has been performed about the correlation between AMD and diabetes mellitus (51). This study showed that in 7 cohort studies, diabetes was shown to be a risk factor for AMD (OR, 1.0.5.; 95 percent CI, 1.0.0.-1.1.4.). Results of 9 cross-sectional studies revealed consistent association of diabetes with AMD (OR, 1.2.1.; 95 percent CI, 1.0.0.-1.4.5.), especially for late AMD (OR, 1.4.8.; 95 percent CI, 1.4.4.-1.5.1.). Similar association was also detected for AMD (OR, 1.2.9.; 95 percent CI, 1.1.3.-1.4.9.) and late AMD (OR, 1.1.6.; 95 percent CI, 1.1.1.-1.2.1.) in 11 case-control studies. However, the authors concluded affirming that the data are not sufficient to state definitely a clear association between these two diseases. Stroke risk has been found to be associated with AMD in a court of patients from

**Table 5.** Results of selected studies investigating the direct correlation between Alzheimer's disease and AMD

| Study and results | References |
|---|---|
| Prevalence of Alzheimer's disease in AMD patients<br>Design: Population-Based cohort study – Sample size: 4,993<br>HR:<br>1.4.4, P<0.0.001　　　in any AMD type<br>1.3.5, P=0.1.61　　　in exudative AMD<br>1.4.4, P<0.0.001　　　in non-exudative AMD | (57) |
| Prevalence of Alzheimer's disease in Advanced AMD patients<br>Design: Population-Based prospective study –<br>Sample size: 6,209<br>OR: 1.5., P=0.3.7 | (8) |
| AD following AMD: Record linkage study of hospital admissions<br>Design: Record-Linkage study<br>OR: 0.8.6<br>Sample size: 65,894<br>Estimated P value: 0.2.2 | (60) |
| AMD following AD: Record linkage study of hospital admissions<br>Design: Record-Linkage study<br>OR: 0.0.4<br>Sample size: 65,894 (AMD) and 168,092 (dementia)<br>Estimated P value: <0.0.001 | (60) |

the Atherosclerosis Risk in Communities Study (ARIC). Multi-variable adjusted hazard ratio (HR) resulted to be 1.5.1., with a greater risk for intracerebral hemorrhage (HR: 2.6.4.) than for cerebral infarction (HR: 1.4.2.) (52). However, an association between AMD and Coronary atherosclerotic heart disease (CHD) or Classical cardiovascular disease (CVD), in people without known risk factors of CVD, has failed to be found (53). Moreover, a novel study performed a meta-regression analysis seeking for an association with incident stroke but no association has been found (54). A recent record linkage study has shown a possible association with obstructive sleep apnea, by recording a RR of 1.4.4. (1.3.2. to 1.5.7.) of AMD following sleep apnea (55). Concerning the link between atherosclerotic pathology and AD, only intracranial atherosclerosis increases substantially the risk of dementia (56).

### 4.2. Studies assessing the direct association between AD and AMD

Recently, several studies were performed in order to better investigate the direct association between AD and AMD (see Table 5). For instance, a population based cohort study conducted in 2015 by Tsai and collegues found AD to be associated significantly with only non-exudative AMD. The authors reported that,

since the database they used was not providing a distinction between PCV and CNV in AMD patients, the lack of significance found in exudative AMD could be due to the protective effect that PCV could have in developing AD, with respect to CNV (57). The absence of a direct association between these two disorders was also documented by Williams and colleagues (58). Another study by Keenan and collaborators based on a cohort of 65,894 people with AMD recruited from English National Health Service and on a dementia cohort (168,092 people) and a reference cohort (more than 7.7. million people) constructed in similar ways, has investigated the risk of AD or dementia following AMD and risk to be admitted for AMD following AD or dementia. This study showed that the risk of AD or dementia following AMD was not elevated. The rate ratio was 0.8.6. (95 percent CI, 0.6.7.-1.0.8.) for AD and 0.9.1. (0.7.9.-1.0.4.) for dementia. The likelihood of being admitted for AMD following AD or dementia was very low: the rate ratio was 0.0.4. (0.0.1.-0.1.0.) for people with AD and 0.0.7. (0.0.4.-0.1.1.) for those with dementia with respect to the reference cohort. The explanation of these results could be that subjects with dementia may be less likely to attend regular optometrist appointments, less likely to notice or report relevant visual symptoms, and, above all, less likely to receive anti-VEGF treatments for exudative AMD, as demonstrated by Curtis and colleagues (59).

The conclusion was that, even if AMD and AD probably share some risk factors and pathophysiological mechanisms, these diseases were not directly associated. However, it could be also due to the possibility that patients with dementia were less likely to receive AMD investigation and treatment (60).

### 5. COMMON PATHOPHYSIOLOGICAL FACTORS

AD is histopathologically characterized by beta-amyloid-containing extracellular senile plaques and hyper-phosphorylated tau-containing intracellular neurofibrillary tangles (NFTs) (61). Both of them are found in the hippocampus and brain cortex (62). The amyloid deposits have been detected also in the inner layers of the retina of AD patients (63). However, retinal amyloid deposits in AD show a different deposition pattern as compared to the classical/neuritic plaques found in the AD patients' brain, possessing a central core with apparently non-radiating fibrils (63).

Amyloid plaques are primarily composed of beta-amyloid protein but different compounds co-localize with it in the brain. We listed the most significant proteins in Table 6. Next to proteins, metal ions including Fe, Zn, Cu, Cr, Ni, Mn, Pb, Si and Al have been found, together with proteoglycans (including heparan, chondroitin, keratin and dermatan sulphate proteoglycans) and immunoglobulins (64).

**Table 6.** Comparison of protein content found in drusen and senile plaques

| Group | Proteins found in drusen | Proteins found in senile plaques | References |
|---|---|---|---|
| Complement | C1q<br>C3, C3d, iC3b<br>C5<br>C8<br>C9<br>CFH<br>CFB<br>Complement Receptor 1<br>C4<br>C5<br>C6<br>MAC | C1q<br>C2<br>C3, C3d, iC3b<br>C9<br>C7<br>MAC<br>CFH<br>CFI<br>CFB | (62,66, 69) |
| Immune system | HLA-DRA<br>Scavenger receptor class B<br>Immunoglobulin lambda chains | HLA-DRA | (62,66, 69) |
| Amyloid | SAP<br>SAA1<br>Amyloid Beta<br>Transthyretin | Transthyretin<br>Amyloid Beta<br>SAP<br>SAA1 | (62,66, 69) |
| Lipid transport | ApoE<br>ApoB | ApoE<br>ApoB | (62,66, 69) |
| Inflammatory | Vitronectin<br>Clusterin<br>TIMP3<br>CRP | CRP<br>Clusterin<br>Vitronectin | (62,66, 69) |
| Other | Serum Albumin<br>Tau<br>MCP<br>ATP synthase<br>Enolase<br>Alfa-1-antichimotrypsin<br>Alfa-1-antitrypsin<br>Retinal dehydrogenase 5<br>Ubiquitin<br>A2E<br>AGE<br>Alfa-2-macroglobulin<br>Acetylcholinesterase | Alfa-1-antichimotrypsin<br>Alfa-1-antitrypsin<br>ATP synthase<br>Enolase<br>Retinal dehydrogenase 5<br>Ubiquitin<br>AGE<br>A2E<br>CLAC<br>Tau<br>Alfa-2 macroglobulin<br>Serum Albumin | (62,66, 69) |

Drusen, the hallmark of AMD, are instead amorphic extracellular deposits containing lipids and proteins along with an increasing list of macromolecules. They lie between the RPE and Bruch's membrane. Drusen can be classified as hard and soft drusen. Hard drusen are focal thickening of the basement membrane of RPE while soft drusen are thickenings limited to the separation of the basement membrane from Bruch's membrane at the inner collagenous zone. Pseudodrusen, instead, are deposits located above the basement membrane of RPE and their presence could be a sign of progression to more advanced stages of AMD (65). A study performed on 36 eye samples found the lipid component to account for around 40 percent of the drusen volume and for the majority of their weight. Proteins are thought to account for most of the volume in drusen (66). Most of the lipids component of drusen was constituted by esterified cholesterol and phosphatidylcholine. Lipid-containing particles were the elements accounting for up to 40 percent of the drusen volume (66). A more recent study found 7-ketocholesterol as a component related to aging and highly represented in drusen (67). This finding is consistent with a model which tries to explain the question of the source of lipids found in retinal depositions by proposing a mechanism in which oxidation products of cholesterol, oxysterols (as 7-ketocholesterol), could gain access to the eye. Another oxysterol, 27-hydroxycholesterol, is significantly present in drusen and its presence has been correlated

with beta-amyloid deposition (68). In drusen, the presence of elements as $Zn^{2+}$, $Fe^{3+}$, $Cu^{2+}$ has been identified (62) and several studies have found lipofuscin to occur in these lesions, suggesting an important role in the pathogenesis (69). Drusen are more typical of dry AMD, especially at the early and intermediate stages, when GA is not yet present. A small number of hard drusen, provided they are smaller than a threshold size (less than 63-um diameter), is considered as a normal sign of aging. Interestingly, drusen volume, analyzed with modern SD-OCT is a biomarker useful to evaluate intermediate AMD progression and the likelihood to develop advanced AMD (70,71). However, in AMD and other types of macular degeneration, the role of these deposits is controversial and it is unclear whether they are causing the RPE dysfunction or are a consequence of the impairment of the RPE function. The hypothesis of an impairment of the nutrients transport across Bruch's membrane by drusen is strengthened by a recent finding which identified aquaporin proteins (AQP1) to be upregulated only in the RPE above drusen. The authors of the study proposed this as a compensatory mechanism to increase the fluid transport impaired by the presence of drusen (72).

Likewise, today, the correct interpretation of amyloid plaques and NFTs in AD is not completely clear (*for review see* (73)). It was shown, for example, that toxicity of A beta was linked to fibril formation (74). The A beta *in vitro* toxicity was linked to several mechanisms, including induction of apoptosis (75), promotion of inflammatory mediators (76), and oxidative stress (77). Phosphorylated tau also exerts its *in vitro* toxicity by similar properties (78). On the other hand, it has been speculated that the two AD hallmarks are the visible non-toxic epiphenomenon of the real pathophysiological process that is, incidentally, invisible and impossible to verify by direct observation (e.g. synaptic damage mediated by soluble toxic intermediates). This process is probably due to oxidative stress (79) and neuroinflammation (80).

## 5.1. Role of beta-amyloid

The amyloids plaques and drusen share common molecular constituents, like beta-amyloid, vitronectin, apolipoprotein E complement components and inflammatory mediators (81); *for review see* (3). In both AD and AMD pathology, the presence of amyloid precursors and amyloid proteins, as well as tau proteins, has been surmised and, to a certain extent, confirmed for decades (82,83). These finding gave rise to the suspicion that AMD pathogenesis could share some features with Alzheimer's disease. In the following years, along with the attempts to fully characterize the proteomics of drusen and sub-RPE deposits, also the characteristics and the pattern of deposition of amyloid in such locations ha been investigated (62). Dentchev and colleagues identified drusen containing beta-amyloid just in AMD patients' eyes and not in normal retinas; moreover, they found

the number of beta-amyloid positive drusen correlated with the stage of the disease and the coexistence of geographic atrophy (GA) (84).

Secreted beta-amyloid exists in mainly two isoforms: A beta 1-40 and A beta 1-42 forms, with the latter being more prevalent in AD. In AMD it is still unclear which of the two isoforms is the most prevalent in drusen, but A beta 1-42 reduced levels in plasma have been found to be correlated with the severity of AMD (85), while physiologically A beta 1-40 is the most prevalent isoform in both vitreous and aqueous humour (62). Amyloid aggregates according to a peculiar pattern in drusen and forms "amyloid vesicles" ranging from 2 to 10 um of diameter. In these vesicles, non-fibrillar oligomers appeared to be the most prevalent component. These vesicles appeared to have an interior substructure with flocculent material and concentric ring-like elements, while mature amyloid fibrils have been found to constitute the outer shell of the vesicles. Another pattern of amyloid deposition in drusen was represented by "amyloid cores" which are thought to be the generating form of the lesions and thus did not co-localize with amyloid vesicles. Amyloid cores have shown immunoreactivity in the central part of drusen and in the region close to the inner collagenous layer of Bruch's membrane (62). Beta-amyloid is known to have proinflammatory effects on the retina (65) and the same holds true for the brain where it strongly activates the microglia (64). It is thought that-beta- amyloid could activate the NLRP3 inflammasome and, in histology sections of AMD specimens, it co-localizes with sites of complement activation (65). Besides this, beta-amyloid could be a proangiogenic factor by inhibiting PEDF (65).

## 5.2. Oxidative stress

As previously discussed, aging is the most important risk factor for both AD and AMD.

The fundamental mechanism of aging is oxidative stress (86). In the brain, oxidative stress is needed for physiological cell functions but when it goes over a certain threshold, it begins to be cytotoxic. Nevertheless, the brain possesses a counter-acting system able to reestablish homeostasis: the dysfunction of this control system could contribute to AD pathophysiology. The excess of the chronic oxidative stress causes a severe neuroinflammation. Lipids mediators, as docosanoids, are thought to play an important role in the contrast of the neuroinflammation; thus, a sluggish synthesis of them could be one of the mechanisms implicated in AD pathology (87).

An excess of oxidative stress in the brain can be caused by mitochondrial leakage but the most abundant source of free radical is thought to derive from the microglial over-activation (88). It has been speculated that oxidative stress is perhaps the earliest feature of AD and a sensitive marker of oxidative stress, heme-oxygenase-1,

has been found elevated in postmortem brain tissue of individuals with both AD and mild cognitive impairment (MCI). Oxidative damage marked by lipid peroxidation, nitration, reactive carbonyls, and nucleic acid oxidation is increased in vulnerable neurons in AD (8). Likewise, morphologic analysis of human donor eyes affected by AMD revealed a decrease in the number of mitochondria per cross-sectional area as compared to expected age-related changes. Mitochondrial DNA (mtDNA) is more susceptible than nuclear DNA to damage from oxidation and blue light. It has been supposed that the impairment of the function of mtDNA-encoded subunits of the electron transport chain may evoke increased superoxide anion production; it causes further mtDNA damage and superoxide anion production (8). Interestingly, autophagy and lysosomal processes linked to oxidative stress are increased in AMD eyes (5) and AD brain (89). Moreover, an oxysterol, 27-Hydroxycholesterol, appears to be implicated in oxidative damage both in AMD and AD. It would act by increasing the generation of reacting oxygen species (ROS) and the production of beta-amyloid (68). In AMD, the RPE affected by chronic oxidative stress is known to release complement coated exosomes which would bind CFH. This mechanism impairs the capacity of CFH to limit the toxic effect of malondialdehyde, a by-product of the metabolism of membrane lipids exposed to constant light and O2 high concentrations (5). Furthermore, the induction of heme-oxigenase 1 (HO-1) (a protein stimulating the oxidation of cholesterol to oxysterols) is suggested to be an early event in the pathogenesis of sporadic AD. Interestingly, HO-1 levels were also increased in RPE of AMD-affected maculas (68).

In conclusion, taken together, increased oxidative stress, mitochondrial and lysosomal dysfunctions seem to be common pathophysiological events in both AMD and AD pathogenesis (8).

### 5.3. Neuroinflammation

Complement activation is a central mechanism in both AMD and AD models of pathology, but while in AD the classical pathway is thought to play a major role, in AMD the alternative pathway is the most involved (88). It has been suggested that amyloid plaques are preferentially placed in areas of micro-hemorrhages in which the blood brain barrier is most likely compromised: it allows an invasion of inflammatory elements (macrophages, microglia) into the tissues. In situ hybridization studies on AMD models have than shown that invading macrophages express C3, so causing further cell damage. This aspect could contribute to the progression of the disease (90). Moreover, both amyloid-proteins and lipofuscin increase in normal eyes and brain as age-related changes (62,65) and it is known these molecules can act as stimulators of the inflammasome, the complement system and autophagy. Aggregated beta-amyloid is an activator of the complement system in the brain as well, where it also works as an activator of the microglia. This causes an increase of oxidative damage as well (88). Microglial activation has been found to be present also around drusen and in the subretinal space (91). Finally, it is well known that aging causes the decrease of hydraulic conductivity in Bruch's membrane and changes in lipid content in the retina (65). Parallel to age, chronic oxidative stress can induce RPE senescence, as when it is exposed to most of risk factors for AMD. These phenomena together are probably the cause and the consequence of beta-amyloid production. In this way, an irreversible positive-feedback mechanism of proinflammatory cytokines and proteases secretion takes place. This process could be the drive of progression of the disease (92).

## 6. CLINICAL TRIALS

Given the supposed link between AD and AMD, both at biomolecular and epidemiological level, some trials have been performed to test drugs able to contrast simultaneously the core symptoms of these two disorders. In particular, in two double-blind randomized trials, the possible effects on cognitive and visual functions of oral supplementation with antioxidant nutrients were studied in both patients with AD and AMD. In the first one, (the Age-Related Eye Disease Study 2 (AREDS2)), retinal specialists in 82 US academic and community medical centers enrolled old AMD subjects from October 2006 to December 2012 (93). In addition to annual eye examinations, several cognitive tests were administered via telephone at baseline and every 2 years during the 5-year follow-up. Some antioxidant nutrients, such as long-chain polyunsaturated fatty acids (1 g) and/or lutein (10 mg)/zeaxanthin (2 mg) vs placebo were tested in this factorial designed trial. All participants were also given varying combinations of vitamins C, E, beta-carotene and zinc. In this study, the oral supplementation with these antioxidant nutrients did not show any significant effect on cognitive functions in patients diagnosed with AMD.

The second trial, instead, has investigated the impact of supplementation with macular carotenoids on macular pigment, vision and cognitive function in patients diagnosed with AD (94). In this double-blind randomized trial, a mix of 10 mg meso-zeaxanthin, 10 mg lutein and 2 mg zeaxanthin was compared to placebo (sun flower oil) in 31 AD patients and 31 age-matched controls. The results confirmed the inefficacy of this kind of supplementation from the cognitive point of view both in AD and control groups, while it was able to improve visual functions (in particular, the contrast sensitivity) in two groups and to widen macular pigment, as measured with dual-wavelength autofluorescence, in AD patients. These results support the hypothesis that antioxidant supplementation could have a positive impact on visual function, but not on cognitive performance in AD patients. Of course, further studies will be necessary to verify these findings.

Finally, since the pre-clinical evidence of the efficacy of glatiramer acetate in AD mice model in reducing amyloid plaques (95) and given the similarity between AD and AMD, this drug was tested vs placebo within a very small randomized trial, in over 50 patients with dry age- related macular degeneration (96). This study showed a significant reduction of drusen as measured by Image-Pro software in the four AMD patients treated with glatiramer acetate, while no difference was observed in the two AMD subjects who received placebo. The results of this small clinical trial, together with the above mentioned pre- clinical evidence on glatiramer efficacy in AD mice model, suggest the usefulness of testing in the future this therapy in both disorders within large double- blind controlled randomized clinical trials.

## 7. CONCLUSIONS

According to the evidence available so far, it is possible to state that AD and AMD, two diseases recognizing aging as the main risk factor, share several aspects.

The presence of retinal beta-amyloid deposits both in AD and AMD patients has been well demonstrated. This finding could represent the basis for assessing the efficacy of anti-amyloid drugs not only in ADbut also in AMD patients. Interestingly, these two diseases also share other molecular aspects, i.e. oxidative stress and neuroinflammation, thus reinforcing the possibility to find common therapeutic strategies.

At the genetic level, polymorphisms of genes related to inhibition of endopeptidases (CST3), complement system (CFH) and inflammatory response (ARMS/HTRA1) have been shown to increase the risk for both disorders. To this respect, a quite intriguing role is played by APOE isoforms. As well documented, in AD APOE epsilon-4 represents the main genetic risk factor, while APOE epsilon-2 represents a protective factor. According to the data available so far, the opposite holds true for AMD, where APOE epsilon-2 plays the role of risk factor and APOE epsilon-4 is a protective factor. The possible explanation for the "inverted" role of these APOE isoforms remains to be understood.

Hypertension, diabetes mellitus, obesity, and excessive alcohol consumption represent other risk factors common to the two disorders, although data on a direct association – i.e. increased risk of AMD in AD or vice versa - are not significant. Oxidative stress is a well-documented pathogenetic factor both in AMD and AD. Clinical trials aimed at assessing the efficacy of antioxidant agents both on visual and cognitive performance in AMD and AD are partly available and in progress.

According to the aging of the population, both AMD and AD will increase their prevalence in the next future. Therefore, the definite knowledge of the overlapping area between the two disorders is of utmost importance, since it will increase the possibility to activate effective preventive strategies for both AMD and AD.

## 9. REFERENCES

1. R.D. Jager, W.F. Mieler, J.W. Miller. Age-related macular degeneration. *N Engl J Med* 358, 2606-2617 (2008)
DOI: 10.1056/NEJMra0801537

2. R. Brookmeyer, E. Johnson, K. Ziegler-Graham, HM Arrighi. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement* 3,186-191 (2007)
DOI: 10.1016/j.jalz.2007.04.381

3. E. Çerman, M. Eraslan, O. Çekiç. Age-related macular degeneration and Alzheimer disease. *Turkish J Med Sci* 45, 1004-1009 (2015)
DOI: 10.3906/sag-1406-146

4. D.H. Anderson, K.C. Talaga, A.J. Rivest, E. Barron, G.S. Hageman, L.V. Johnson. Characterization of beta amyloid assemblies in drusen: the deposits associated with aging and age-related macular degeneration. *Exp Eye Res* 78, 243-256 (2004)
DOI: 10.1016/j.exer.2003.10.011

5. H. Zając-Pytrus, A. Pilecka, Turno-Kręcicka, J. Adamiec-Mroczek, M. Misiuk-Hojło. The Dry Form of Age-Related Macular Degeneration (AMD): The Current Concepts of Pathogenesis and Prospects for Treatment. *Adv Clin Exp Med* 24, 1099-1104 (2015)
DOI: 10.17219/acem/27093

6. M. Reinisalo, A. Kårlund, A. Koskela, K. Kaarniranta, R.O. Karjalainen. Polyphenol Stilbenes: Molecular Mechanisms of Defence against Oxidative Stress and Aging-Related Diseases. *Oxid Med Cell Longev* 2015, 1-24 (2015)
DOI: 10.1155/2015/340520

7. R.B. Nussenblatt, B. Liu, L. Wei, H.N. Sen. The immunological basis of degenerative diseases of the eye. *Int Rev Immunol* 32, 97-112 (2013)

DOI: 10.3109/08830185.2012.740536

8. K. Kaarniranta, A. Salminen, A. Haapasalo, H. Soininen, M. Hiltunen. Age-related macular degeneration (AMD): Alzheimer's disease in the eye? *J Alzheimer's Dis* 24, 615-631 (2011)
DOI: 10.3233/JAD-2011-101908

9. Age-related Eye Disease Study Research Group A-REDSR. Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. Ophthalmology 107, 2224-2232 (2000)
DOI: 10.1016/S0161-6420(00)00409-7

10. P.L. Tan, C. Bowes Rickman, N. Katsanis. AMD and the alternative complement pathway: genetics and functional implications. *Hum Genomics* 10, 23 (2016)
DOI: 10.1186/s40246-016-0079-x

11. A.P. Ciardella, I.M. Donsoff, S.J. Huang, D.L. Costa, L.A. Yannuzzi. Polypoidal choroidal vasculopathy. *Surv Ophthalmol* 49, 25-37 (2004)
DOI: 10.1016/j.survophthal.2003.10.007

12. C. Reitz, R. Mayeux. Alzheimer disease: epidemiology, diagnostic criteria, risk factors and biomarkers. *Biochem Pharmacol* 88, 640-51 (2014)
DOI: 10.1016/j.bcp.2013.12.024

13. M. Baumgart, H.M. Snyder, M.C. Carrillo, S. Fazio, H. Kim, H. Johns. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimers Dement* 11, 718-726 (2015)
DOI: 10.1016/j.jalz.2015.05.016

14. M. Prince, M. Guerchet, M. Prina. The Global Impact of Dementia 2013-2050. *Alzheimer's Dis Int London* (2013)

15. M.C. Polidori, M. Marvardi, A. Cherubini, U. Senin, P. Mecocci. Heart disease and vascular risk factors in the cognitively impaired elderly: implications for Alzheimer's dementia. *Aging (Milano)* 13, 231-239 (2001)
DOI: 10.1007/bf03351481

16. J.A. Schneider, P.A. Boyle, Z. Arvanitakis, J.L Bienias, D.A. Bennett. Subcortical infarcts, Alzheimer's disease pathology, and memory function in older persons. *Ann Neurol* 62, 59-66 (2007)

17. R.N. Kalaria, C. Ballard. Overlap between pathology of Alzheimer disease and vascular dementia. *Alzheimer Dis Assoc Disord* 13 Suppl 3, S115-123 (1999)
DOI: 10.1097/00002093-199912003-00017

18. M. Ganguli, W.A. Kukull. Lost in Translation. *Arch Neurol* 67, 107 (2010)
DOI: 10.1001/archneurol.2009.311

19. The Eye Diseases Prevalence Research Group*. Causes and prevalence of visual impairment among adults in the united states. *Arch Ophthalmol* 122, 477-485 (2004)
DOI: 10.1001/archopht.122.4.477

20. A. Laitinen, L. Laatikainen, T. Harkanen, S. Koskinen, A. Reunanen, A. Aromaa. Prevalence of major eye diseases and causes of visual impairment in the adult Finnish population: A nationwide population-based survey. *Acta Ophthalmol* 88, 463-471 (2010)
DOI: 10.1111/j.1755-3768.2009.01566.x

21. M.A. Bamashmus, B. Matlhaga, G.N. Dutton. Causes of blindness and visual impairment in the West of Scotland. *Eye (Lond)* 18, 257-261 (2004)
DOI: 10.1038/sj.eye.6700606

22. J.R. Evans, A.E. Fletcher, R.P.L. Wormald, Community MRCT of A and M of OP in the. Causes of visual impairment in people aged 75 years and older in Britain: an add-on study to the MRC Trial of Assessment and Management of Older People in the Community. *Br J Ophthalmol* 88, 365-370 (2004)
DOI: 10.1136/bjo.2003.019927

23. D.S. Friedman, B.J. O'Colmain, B. Muñoz, S.C. Tomany, C. McCarty, P.T.V.M. de Jong, B. Nemesure, P. Mitchell, J. Kempen, Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol* 122, 564-572 (2004)
DOI: 10.1001/archopht.122.4.564

24. W.L. Wong, X. Su, X. Li, C.M.G. Cheung, R. Klein, C.Y. Cheng, T.Y. Wong. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. *Lancet Glob Heal* 2, e106-e116 (2014)

DOI: 10.1002/ana.21142

DOI: 10.1016/S2214-109X(13)70145-1

25. H.R. Coleman, C-C. Chan, F.L. Ferris, E.Y. Chew. Age-related macular degeneration. *Lancet (London, England)* 372, 1835-1845 (2008)
DOI: 10.1016/S0140-6736(08)61759-6

26. C.W. Wong, Y. Yanagi, W-K. Lee, Y. Ogura, I. Yeo, T.Y. Wong, C.M.G. Cheung. Age-related macular degeneration and polypoidal choroidal vasculopathy in Asians. *Prog Retin Eye Res* 53, 107-139 (2016)
DOI: 10.1016/j.preteyeres.2016.04.002

27. R. Mayeux, Y. Stern. Epidemiology of Alzheimer Disease. *Cold Spring Harb Perspect Med* 2, 1-2(8) (2012)
DOI: 10.1101/cshperspect.a006239

28. A.R. Rudnicka, Z. Jarrar, R. Wormald, D.G. Cook, A. Fletcher, C.G. Owen. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: A meta-analysis. *Ophthalmology* 119, 571-580 (2012)
DOI: 10.1016/j.ophtha.2011.09.027

29. B.C. Riedel, P.M. Thompson, R.D. Brinton. Age, APOE and sex: Triad of risk of Alzheimer's disease. *J Steroid Biochem Mol Biol* 160, 134-147 (2016)
DOI: 10.1016/j.jsbmb.2016.03.012

30. J.M. Seddon, J. Cote, W.F. Page, S.H. Aggen, M.C. Neale. The US twin study of age-related macular degeneration: relative roles of genetic and environmental influences. *Arch Ophthalmol* (Chicago, Ill 1960) 123, 321-327 (2005)
DOI: 10.1001/archopht.123.3.321

31. J.N. Cooke Bailey, J.D. Hoffman, R.J. Sardell, W.K. Scott, M.A. Pericak-Vance, J.L Haines. The Application of Genetic Risk Scores in Age-Related Macular Degeneration: A Review. *J Clin Med* 5, 31 (2016)
DOI: 10.3390/jcm5030031

32. P.N. Baird, E. Guida, D.T. Chu, H.T.V. Vu, R.H. Guymer. The epsilon2 and epsilon4 alleles of the apolipoprotein gene are associated with age-related macular degeneration. *Invest Ophthalmol Vis Sci* 45, 1311-1315 (2004)
DOI: 10.1167/iovs.03-1121

33. M.W. Logue, M. Schu, B.N. Vardarajan, J. Farrell, K.L Lunetta, G. Jun, C.T. Baldwin, M.M. DeAngelis, L.A. Farrer. A search for age-related macular degeneration risk variants in Alzheimer disease genes and pathways. *Neurobiol Aging* 35, 1510 (2014)
DOI: 10.1016/j.neurobiolaging.2013.12.007

34. A.N. Tsiloulis, F. Zacharaki, M.G. Kotoula, D.Z. Chatzoulis, M.A. Morrison, K. Mayne, E. Dardiotis, I.L Stefanidis, P. Almpanidou, M.M. DeAngelis, E.E. Tsironi. Genetic variants in complement pathway and ARMS2/HTRA1 genes and risk of age-related macular degeneration in a homogeneous population from central Greece. *Ophthalmic Genet* 1-6 (2016)
DOI: 10.3109/13816810.2015.1045525

35. S.J. Woo, J. Ahn, M.A. Morrison, S.Y. Ahn, J. Lee, K.W. Kim, M.M. DeAngelis, K.H. Park. Analysis of genetic and environmental risk factors and their interactions in Korean patients with age-related macular degeneration. *PLoS One* 10, 1-14 (2015)
DOI: 10.1371/journal.pone.0132771

36. M. Zetterberg, S. Landgren, M.E. Andersson, M.S. Palmér, D.R Gustafson, I. Skoog, L. Minthon, D.S Thelle, A. Wallin, N. Bogdanovic, N. Andreasen, K. Blennow, H. Zetterberg. Association of complement factor H Y402H gene polymorphism with Alzheimer's disease. *Am J Med Genet B Neuropsychiatr Genet* 147B, 720-726 (2008)
DOI: 10.1002/ajmg.b.30668

37. J.M. Seddon, R. Reynolds, Y. Yu, M.J. Daly, B. Rosner. Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors. *Ophthalmology* 118, 2203-2211 (2011)
DOI: 10.1016/j.ophtha.2011.04.029

38. P. Proitsi, M.K. Lupton, F. Dudbridge, M. Tsolaki, G. Hamilton, M. Daniilidou, M. Pritchard, K. Lord, B.M. Martin, D. Craig, S Todd, B McGuinness, P Hollingworth, D Harold, I Kloszewska, H Soininen, P. Mecocci, B Velas, M Gill, B Lawlor, DC Rubinsztein, C Brayne, PA Passmore, J Williams, S Lovestone, JF Powell. Alzheimer's disease and age-related macular degeneration have different genetic models for complement gene variation. *Neurobiol Aging* 33, 1843 (2012)
DOI: 10.1016/j.neurobiolaging.2011.12.036

39. B.N. Vardarajan, Y. Zhang, J.H. Lee, R. Cheng, C. Bohm, M. Ghani, C. Reitz, D.

Reyes-Dumeyer, Y. Shen, E. Rogaeva, St George-Hyslop P, R. Mayeux. Coding mutations in SORL1 and Alzheimer disease. *Ann Neurol* 77, 215-227 (2015)
DOI: 10.1002/ana.24305

40. J.M. Butler, U. Sharif, M. Ali, M. McKibbin, J.P Thompson, R. Gale, Y.C. Yang, C. Inglehearn, L. Paraoan. A missense variant in CST3 exerts a recessive effect on susceptibility to age-related macular degeneration resembling its association with Alzheimers disease. *Hum Genet* 705-715 (2015)
DOI: 10.1007/s00439-015-1552-7

41. J.D. Hoffman, M.J.J.P. van Grinsven, C. Li, M Brantley, J McGrath, A Agarwal, WK Scott, SG Schwartz, J Kovach, M Pericak-Vance, CI Sanchez, JL Haines. Genetic Association Analysis of Drusen Progression. *Investig Opthalmology Vis Sci* 57, 2225 (2016)
DOI: 10.1167/iovs.15-18571

42. R Klein, BE Klein, SE Moss. Relation of smoking to the incidence of age-related maculopathy. The Beaver Dam Eye Study. *Am J Epidemiol* 147,103-110 (1998)
DOI: 10.1093/oxfordjournals.aje.a009421

43. B Neuner, A Komm, J Wellmann, M Dietzel, D Pauleikhoff, J Walter, M Busch, H-W Hense. Smoking history and the incidence of age-related macular degeneration--results from the Muenster Aging and Retina Study (MARS) cohort and systematic review and meta-analysis of observational longitudinal studies. *Addict Behav* 34, 938-947 (2009)
DOI: 10.1016/j.addbeh.2009.05.015

44. TE Clemons, RC Milton, R Klein, JM Seddon, FL Ferris, Age-Related Eye Disease Study Research Group. Risk factors for the incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19. Ophthalmology 112, 533-539 (2005)
DOI: 10.1016/j.ophtha.2004.10.047

45. W Xu, L Tan, H-F Wang, T Jiang, M-S Tan, L Tan, Q-F Zhao, J-Q Li, J Wang, J-T. Yu Meta-analysis of modifiable risk factors for Alzheimer's disease*. J Neurol Neurosurg Psychiatry* 86, 1299-1306 (2015)
DOI: 10.1136/jnnp-2015-310548

46. J Ye, Y-F Xu, J-J He, L-X Lou. Association between aspirin use and age-related macular degeneration: a meta-analysis. *Invest Ophthalmol Vis Sci* 55, 2687-2696 (2014)
DOI: 10.1167/iovs.13-13206

47. VK Katsi, ME Marketou, DA Vrachatis, AJ Manolis, P Nihoyannopoulos, D Tousoulis, PE Vardas, I Kallikazaros. Essential hypertension in the pathogenesis of age-related macular degeneration: a review of the current evidence. *J Hypertens* 33, 2382-2388 (2015)
DOI: 10.1097/HJH.0000000000000766

48. R Klein, CE Myers, GHS Buitendijk, E Rochtchina, X Gao, PTVM de Jong, TA Sivakumaran, G Burlutsky, R McKean-Cowdin, A Hofman, SK Iyengar, KE Lee, BH Stricker, JR Vingerling, P Mitchell, BE Klein, CC Klaver, JJ Wang. Lipids, lipid genes, and incident age-related macular degeneration: the three continent age-related macular degeneration consortium. *Am J Ophthalmol* 158, 513-524 (2014)
DOI: 10.1016/j.ajo.2014.05.027

49. Z Arvanitakis, RS Wilson, JL Bienias, DA Evans, DA Bennett, Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function. *Arch Neurol* 61, 661 (2004)
DOI: 10.1001/archneur.61.5.661

50. EL Abner, PT Nelson, RJ Kryscio, FA Schmitt, DW Fardo, RL Woltjer, NJ Cairns, L Yu, HH Dodge, C Xiong, K Masaki, SL Tyas, DA Bennett, JA Schneider, Z Arvanitakis. Diabetes is associated with cerebrovascular but not Alzheimer neuropathology. *Alzheimers Dement* 12(8), 882-889 (2016)
DOI: 10.1016/j.jalz.2015.12.006

51. X Chen, SS Rong, Q Xu, FY Tang, Y Liu, H Gu, POS Tam, LJ Chen, ME Brelén, CP Pang, C Zhao Diabetes mellitus and risk of age-related macular degeneration: a systematic review and meta-analysis. *PLoS One* 9(9), e108196 (2014)
DOI: 10.1371/journal.pone.0108196

52. MK Ikram, P Mitchell, R Klein, AR Sharrett, DJ Couper, TY Wong. Age-related macular degeneration and long-term risk of stroke subtypes. Stroke 43, 1681-1683 (2012)
DOI: 10.1161/STROKEAHA.112.654632

53. AB Fernandez, TY Wong, R Klein, D Collins, G Burke, MF Cotch, B Klein, MM Sadeghi, Chen J. Age-Related Macular Degeneration and Incident Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis. Ophthalmology 119, 765-770 (2012)

DOI: 10.1016/j.ophtha.2011.09.044

54. AB Fernandez, GA Panza, B Cramer, S Chatterjee, R Jayaraman, W-C Wu. Age-Related Macular Degeneration and Incident Stroke: A Systematic Review and Meta-Analysis. *PLoS One* 10, e0142968 (2015)
DOI: 10.1371/journal.pone.0142968

55. TDL Keenan, R Goldacre, MJ Goldacre. Associations between obstructive sleep apnoea, primary open angle glaucoma and age-related macular degeneration: record linkage study. *Br J Ophthalmol,* bjophthalmol-2015-308278 (2016)
DOI: 10.1136/bjophthalmol-2015-308278

56. H Dolan, B Crain, J Troncoso, SM Resnick, AB Zonderman, RJ Obrien. Atherosclerosis, dementia, and Alzheimer disease in the Baltimore Longitudinal Study of Aging cohort. *Ann Neurol* 68, 231-240 (2010)
DOI: 10.1002/ana.22055

57. D-C Tsai, S-J Chen, C-C Huang, M-K Yuan, H-B Leu. Age-Related Macular Degeneration and Risk of Degenerative Dementia among the Elderly in Taiwan. Ophthalmology 122, 2327-2335 (2015)
DOI: 10.1016/j.ophtha.2015.07.033

58. MA Williams, V Silvestri, D Craig, AP Passmore, G Silvestri. The prevalence of age-related macular degeneration in Alzheimer's disease. *J Alzheimers Dis* 42, 909-914 (2014)
DOI: 10.3233/JAD-140243

59. LH Curtis, BG Hammill, LG Qualls, LD Dimartino, F Wang, KA Schulman, SW Cousins. Treatment Patterns for Neovascular Age-Related Macular Degeneration: Analysis of 284 380 Medicare Beneficiaries. *Am J Ophthalmol* 153, 1116-1124 (2012)
DOI: 10.1016/j.ajo.2011.11.032

60. TDL Keenan, R Goldacre, MJ Goldacre. Associations between age-related macular degeneration, Alzheimer disease, and dementia: record linkage study of hospital admissions. *JAMA Ophthalmol* 132, 63-68 (2014)
DOI: 10.1001/jamaophthalmol.2013.5696

61. P Tiraboschi, LA Hansen, LJ Thal, J Corey-Bloom. The importance of neuritic plaques and tangles to the development and evolution of AD. Neurology 62, 1984-1689 (2004)
DOI: 10.1212/01.WNL.0000129697.01779.0A

62. K Ohno-Matsui. Parallel findings in age-related macular degeneration and Alzheimer's disease. *Prog Retin Eye Res* 30, 217-238 (2011)
DOI: 10.1016/j.preteyeres.2011.02.004

63. M Koronyo-hamaoui, Y Koronyo, A V Ljubimov, A Carol, MK Ko, KL Black, M Schwartz, DL Farkas. Plaques in a Mouse Model 1-27 (2012)
DOI: 10.1016/j.neuroimage.2010.06.020. Identification

64. CS Atwood, RN Martins, MA Smith, G Perry. Senile plaque composition and posttranslational modification of amyloid-beta peptide and associated proteins. Peptides 23, 1343-1350 (2002)
DOI: 10.1016/S0196-9781(02)00070-0

65. JW Miller. Age-related macular degeneration revisited - Piecing the puzzle: The LXIX edward jackson memorial lecture. *Am J Ophthalmol* 155, 1-35 (2013)
DOI: 10.1016/j.ajo.2012.10.018

66. L Wang, ME Clark, DK Crossman, K Kojima, JD Messinger, JA Mobley, CA Curcio. Abundant Lipid and Protein Components of Drusen. *PLoS One* 5 (2010)
DOI: 10.1371/journal.pone.0010329

67. IR Rodriguez, ME Clark, JW Lee, CA Curcio. 7-ketocholesterol accumulates in ocular tissues as a consequence of aging and is present in high levels in drusen. *Exp Eye Res* 128, 151-155 (2014)
DOI: 10.1016/j.exer.2014.09.009

68. J.R. Dasari Prashanthi, G Marwarha., B.B Singh., O. B Ghribi. The oxysterol 27-hydroxycholesterol increases b-amyloid and oxidative stress in retinal pigment epithelial cells. *BMC Ophthalmol* 10, 1e12 (2010)
DOI: 10.1186/1471-2415-10-22

69. C Bowes Rickman, S Farsiu, CA Toth, M Klingeborn. Dry Age-Related Macular Degeneration: Mechanisms, Therapeutic Targets, and Imaging. *Investig Opthalmology Vis Sci* 54 Dec 13;54(14) (2013)
DOI: 10.1167/iovs.13-12757

70. FG Schlanitz, B Baumann, M Kundi, S Sacu, M Baratsits, U Scheschy, A Shahlaee, TJ Mittermüller, A Montuoro, P Roberts, M Pircher, CK Hitzenberger, U Schmidt-Erfurth. Drusen volume development over time and

its relevance to the course of age-related macular degeneration. *Br J Ophthalmol*, bjophthalmol-2016-308422 (2016)
DOI: 10.1136/bjophthalmol-2016-308422

71. NS Abdelfattah, H Zhang, DS Boyer, PJ Rosenfeld, WJ Feuer, G Gregori, SR Sadda. Drusen Volume as a Predictor of Disease Progression in Patients With Late Age-Related Macular Degeneration in the Fellow Eye. *Invest Ophthalmol Vis Sci* 57, 1839-1846 (2016)
DOI: 10.1167/iovs.15-18572

72. TL Tran, T Bek, M la Cour, JU Prause, S Hamann, S Heegaard. Aquaporin-1 Expression in Retinal Pigment Epithelial Cells Overlying Retinal Drusen. *Ophthalmic Res* 55:180-184 (2016)
DOI: 10.1159/000443207

73. RJ Castellani, H-G Lee, X Zhu, G Perry, MA Smith. Alzheimer disease pathology as a host response. *J Neuropathol Exp Neurol* 67, 523-531 (2008)
DOI: 10.1097/NEN.0b013e318177eaf4

74. A Lorenzo, BA Yankner. Beta-amyloid neurotoxicity requires fibril formation and is inhibited by congo red. *Proc Natl Acad Sci USA* 91, 12243-12247 (1994)
DOI: 10.1073/pnas.91.25.12243

75. G Forloni, R Chiesa, S Smiroldo, L Verga, M Salmona, F Tagliavini, N Angeretti. Apoptosis mediated neurotoxicity induced by chronic application of beta amyloid fragment 25-35. *Neuroreport* 4, 523-526 (1993)
DOI: 10.1097/00001756-199305000-00015

76. P Eikelenboom, R Veerhuis, W Scheper, AJM Rozemuller, WA van Gool, JJM Hoozemans. The significance of neuroinflammation in understanding Alzheimer's disease. *J Neural Transm* 113, 1685-1695 (2006)
DOI: 10.1007/s00702-006-0575-6

77. RJ Mark, EM Blanc, MP Mattson. Amyloid beta-peptide and oxidative cellular injury in Alzheimer's disease. *Mol Neurobiol* 12, 211-224 (1996)
DOI: 10.1007/BF02755589

78. B Bandyopadhyay, G Li, H Yin, J Kuret. Tau aggregation and toxicity in a cell culture model of tauopathy. *J Biol Chem* 282, 16454-16464 (2007)
DOI: 10.1074/jbc.M700192200

79. A Nunomura, RJ Castellani, X Zhu, PI Moreira, G Perry, MA Smith. Involvement of oxidative stress in Alzheimer disease. J *Neuropathol Exp Neurol* 65, 631-641 (2006)
DOI: 10.1097/01.jnen.0000228136.58062.bf

80. RE Mrak, WST Griffin. Common inflammatory mechanisms in Lewy body disease and Alzheimer disease. *J Neuropathol Exp Neurol* 66, 683-686 (2007)
DOI: 10.1097/nen.0b013e31812503e1

81. JM Isas, V Luibl, L V Johnson, R Kayed, R Wetzel, CG Glabe, R Langen, J Chen. Soluble and mature amyloid fibrils in drusen deposits. *Invest Ophthalmol Vis Sci* 51, 1304-1310 (2010)
DOI: 10.1167/iovs.09-4207

82. KU Löffler, DP Edward, MO Tso. Immunoreactivity against tau, amyloid precursor protein, and beta-amyloid in the human retina. Invest *Ophthalmol Vis Sci* 36, 24-31 (1995)

83. RA Crowther. Structural aspects of pathology in Alzheimer's disease. *Biochim Biophys Acta* 1096, 1-9 (1990)
DOI: 10.1016/0925-4439(90)90004-9

84. T Dentchev, AH Milam, VM-Y Lee, JQ Trojanowski, JL Dunaief. Amyloid-beta is found in drusen from some age-related macular degeneration retinas, but not in drusen from normal retinas. *Mol Vis* 9, 184-190 (2003)
DOI: 10.1016/s0002-9394(03)00804-3

85. R Guymer, T Cipriani, KD Rittenhouse, L Lim, LD Robman, W Li, W Wang, S Deng, P Banerjee. Plasma levels of amyloid beta and other proinflammatory mediators in patients with age-related macular degeneration. *Graefe's Arch Clin Exp* 253, 1347-1354 (2015)
DOI: 10.1007/s00417-015-2970-x

86. D. Harman. Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 11, 298-300 (1956)
DOI: 10.1093/geronj/11.3.298

87. NG Bazan. Is There a Molecular Logic That Sustains Neuronal Functional Integrity and Survival? Lipid Signaling Is Necessary for Neuroprotective Neuronal Transcriptional Programs. *Mol Neurobiol* 50, 1-5 (2014)
DOI: 10.1007/s12035-014-8897-0

88. EG McGeer, A Klegeris, PL McGeer. Inflammation, the complement system and

the diseases of aging. Neurobiology of Aging Dec;26 Suppl 1, 94-97 (2005)
DOI: 10.1016/j.neurobiolaging.2005.08.008

89. Y Cai, J Arikkath, L Yang, M-L Guo, P Periyasamy, S Buch. Interplay of endoplasmic reticulum stress and autophagy in neurodegenerative disorders. Autophagy 12, 225-244 (2016)
DOI: 10.1080/15548627.2015.1121360

90. GJ Kotwal, N Fernando, J Zhou, K. Valter Exploring the potential benefits of vaccinia virus complement control protein in controlling complement activation in pathogenesis of the central nervous system diseases. *Mol Immunol* 61, 204-209 (2014)
DOI: 10.1016/j.molimm.2014.06.022

91. JM Sivak. The aging eye: Common degenerative mechanisms between the Alzheimer's brain and retinal disease. *Investig Ophthalmol Vis Sci* 54, 871-880 (2013)
DOI: 10.1167/iovs.12-10827

92. L Feng, F Wang. Detecting A-beta Deposition and RPE Cell Senescence in the Retinas of SAMP8 Mice. *Discov Med* 21, 149-158 (2016)

93. EY Chew, TE Clemons, E Agrón, LJ Launer, F Grodstein, PS Bernstein, Age-Related Eye Disease Study 2 (AREDS2) Research Group. Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial. JAMA 314, 791-801 (2015)
DOI: 10.1001/jama.2015.9677

94. JM Nolan, E Loskutova, A Howard, R Mulcahy, R Moran, J Stack, M Bolger, RF Coen, J Dennison, KO Akuffo, N Owens, R Power, D Thurnham, S Beatty. The impact of supplemental macular carotenoids in Alzheimer's disease: a randomized clinical trial. *J Alzheimers Dis* 44, 1157-1169 (2015)
DOI: 10.3233/JAD-142265

95. O Butovsky, M Koronyo-Hamaoui, G Kunis, E Ophir, G Landa, H Cohen, M Schwartz. Glatiramer acetate fights against Alzheimer's disease by inducing dendritic-like microglia expressing insulin-like growth factor 1. *Proc Natl Acad Sci USA* 103, 11784-11789 (2006)
DOI: 10.1073/pnas.0604681103

96. G Landa, O Butovsky, J Shoshani, M Schwartz, A Pollack. Weekly vaccination with Copaxone

(glatiramer acetate) as a potential therapy for dry age-related macular degeneration. *Curr Eye Res* 33, 1011-1013 (2008)
DOI: 10.1080/02713680802484637

97. FL Ferris, CP Wilkinson, A Bird, U Chakravarthy, E Chew, K Csaky, SR Sadda. Clinical Classification of Age-related Macular Degeneration. Ophthalmology 120, 844-851 (2013)
DOI: 10.1016/j.ophtha.2012.10.036

98. M Yuzawa. (Polypoidal choroidal vasculopathy). Nihon Ganka Gakkai Zasshi 116, 200-231 (2012)
DOI: 10.4264/numa.71.282

99. T Iida. Polypoidal choroidal vasculopathy with an appearance similar to classic choroidal neovascularisation on fluorescein angiography. *Br J Ophthalmol* 91, 1103-1104 (2007)
DOI: 10.1136/bjo.2007.116160

100. PL McGeer, EG McGeer. Inflammation and the degenerative diseases of aging. in *Ann NY Acad Sci* Dec 1035, 104-116 (2004)
DOI: 10.1196/annals.1332.007

101. GJ McKay, CC Patterson, U Chakravarthy, S Dasari, CC Klaver, JR Vingerling, L Ho, PTVM de Jong, AE Fletcher, IS Young, JH Seland, M Rahu, G Soubrane, L Tomazzoli, F Topouzis, J Vioque, AD Hingorani, R Sofat, M Dean, J Sawitzke, JM Seddon, I Peter, AR Webster, AT Moore, JR Yates, V Cipriani, LG Fritsche, BH Weber, CN Keilhauer, AJ Lotery, S Ennis, ML Klein, PJ Francis, D Stambolian, A Orlin, MB Gorin, DE Weeks, CL Kuo, A Swaroop, M Othman, A Kanda, W Chen, GR Abecasis, AF Wright, C Hayward, PN Baird, RH Guymer, J Attia, A Thakkinstian, G Silvestri. Evidence of association of APOE with age-related macular degeneration - a pooled analysis of 15 studies. *Hum Mutat* 32, 1407-1416 (2011)
DOI: 10.1002/humu.21577

102. PP Connell, PA Keane, EC O'Neill, RW Altaie, E Loane, K Neelam, JM Nolan, S Beatty. Risk factors for age-related maculopathy. *J Ophthalmol* 2009, 360764 (2009)
DOI: 10.1155/2009/360764

103. Q-Y Zhang, L-J Tie, S-S Wu, P-L Lv, H-W Huang, W-Q Wang, H Wang, L Ma. Overweight, Obesity, and Risk of Age-Related Macular Degeneration. *Invest Ophthalmol Vis Sci* 57, 1276-1283 (2016)

DOI: 10.1167/iovs.15-18637

104. A Cougnard-Grégoire, M-N Delyfer, J-F Korobelnik, M-B Rougier, F Malet, M Le Goff, J-F Dartigues, J Colin, P Barberger-Gateau, C. Delcourt Long-term blood pressure and age-related macular degeneration: the ALIENOR study. *Invest Ophthalmol Vis Sci* 54, 1905-1912 (2013)
DOI: 10.1167/iovs.12-10192

105. NE Shepardson, GM Shankar, DJ Selkoe. Cholesterol level and statin use in Alzheimer disease: II. Review of human trials and recommendations. *Arch Neurol* 68, 1385-1392 (2011)
DOI: 10.1001/archneurol.2011.242

106. MN Sabbagh, K Thind, DL Sparks. On cholesterol levels and statins in cognitive decline and Alzheimer disease: progress and setbacks. *Alzheimer Dis Assoc Disord* 23, 303-305 (2009)
DOI: 10.1097/WAD.0b013e3181a80242

107. CR Hooijmans, AJ Kiliaan. Fatty acids, lipid metabolism and Alzheimer pathology. *Eur J Pharmacol* 585, 176-196 (2008)
DOI: 10.1016/j.ejphar.2007.11.081

108. TJ Littlejohns, WE Henley, IA Lang, C Annweiler, O Beauchet, PHM Chaves, L Fried, BR Kestenbaum, LH Kuller, KM Langa, Lopez OL, Kos K, Soni M, Llewellyn DJ. Vitamin D and the risk of dementia and Alzheimer disease. Neurology 83, 920-928 (2014)
DOI: 10.1212/WNL.0000000000000755

109. C Annweiler, M Drouet, GT Duval, P-Y Paré, S Leruez, M Dinomais, D Milea. Circulating vitamin D concentration and age-related macular degeneration: Systematic review and meta-analysis. Maturitas 88, 101-112 (2016)
DOI: 10.1016/j.maturitas.2016.04.002

110. Y-S Ho, D Chun-Hei Poon, T-F Chan, R Chuen-Chung Chang. From Small to Big Molecules: How Do We Prevent and Delay the Progression of Age-Related Neurodegeneration? *Curr Pharm Des* 18, 15-26 (2012)
DOI: 10.2174/138161212798919039

111. ST Pendlebury, PM. Rothwell Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet 8, 1006-1018 (2009)

DOI: 10.1016/S1474-4422(09)70236-4

112. ZS Tan, A Beiser, RS Vasan, R Au, S Auerbach, DP Kiel, PA Wolf, S Seshadri. Thyroid function and the risk of Alzheimer disease: the Framingham Study. *Arch Intern Med* 168, 1514-1520 (2008)
DOI: 10.1001/archinte.168.14.1514

113. L Chaker, GHS Buitendijk, A Dehghan, M Medici, A Hofman, JR Vingerling, OH Franco, CCW Klaver, RP Peeters. Thyroid function and age-related macular degeneration: a prospective population-based cohort study--the Rotterdam Study. *BMC Med* 13, 94 (2015)
DOI: 10.1186/s12916-015-0329-0

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