FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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Diet and age-related macular degeneration

Relação da dieta e estilo de vida com a degenerescência macular relacionada com a idade

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RESUMO

A Degenerescência Macular Relacionada com a Idade (DMI) é uma doença que resulta na perda de visão central. É a causa de cegueira irreversível mais frequente nos países desenvolvidos. De momento, não existem tratamentos convincentes para a DMI por isso a prevenção é um alvo terapêutico vital, especificamente os fatores de risco modificáveis, como o tabaco, a dieta e o estilo de vida.

Com este trabalho, e através da análise da literatura existente, procurou-se perceber o estado de arte relativo à associação da DMI com o tabaco, atividade física e dieta não suplementada, concretamente de antioxidantes como as vitaminas A, E, C e zinco, carotenos como a luteína e zeaxantina e ácidos gordos ómega-3.

Os resultados encontrados de entre vários estudos coorte prospetivos, estudos transversais, de casos-controlo e revisões sistemáticas mostraram evidências convincentes de que antioxidantes, luteína, zeaxantina e ácidos gordos ómega-3 podem reduzir a taxa de progressão para formas tardias da DMI. Além disso, novos estudos parecem sugerir que os grupos de alimentos que contém os nutrientes e dietas completas podem ter uma influência superior na prevenção da DMI.

Podemos concluir que relativamente à prevenção primária e secundária da DMI, devem ser feitas recomendações para aumento da ingestão de antioxidantes, luteína, zeaxantina e ácidos gordos ómega-3, dado que são suportadas por um número razoável de evidências científicas. Relativamente às dietas completas, novas evidências parecem promissoras e novos estudos devem estar disponíveis em breve, para que recomendações melhores e mais específicas possam atingir populações com risco aumentado de DMI. O tabaco é hoje um fator de risco aceite e importante para a DM I e populações em risco ou diagnosticadas recentemente devem ser aconselhadas a parar de fumar.

ABSTRACT

Age-related macular degeneration (AMD) is a medical condition which results in blurred vision or central vision loss. It is the most common cause of irreversible vision loss in developed countries. At the moment, there is no satisfactory treatment so hope relies in prevention of modifiable risk factor, such as smoking, diet and lifestyle.

With this work, we sought out to find the state of art analyzing literature regarding the relationship of smoking, physical activity and non-supplemented diet, specifically antioxidants such as vitamin A, E, C and zinc, carotenes like lutein and zeaxanthin, and omega-3 fatty acids with the incidence of AMD.

Results found through several prospective cohort studies, cross sectional studies, case-control studies and systematic reviews, fairly strong evidence that antioxidants, lutein, zeaxanthin and omega-3 fatty acids may decrease the risk of progression to late forms of the disease. Moreover, new evidence also suggests that food groups containing this nutrients and more importantly whole diet patterns may have even a higher beneficial influence in preventing AMD.

We could conclude that regarding primary and secondary prevention of AMD, dietary recommendations for high intake of antioxidants, lutein, zeaxanthin and omega-3 fatty acids should be made and are supported today by a fairly good amount of research literature. Regarding whole diet patterns, new evidence looks more promising than any other and more studies should be available soon, so better food intake recommendations can reach populations at risk for AMD. Smoking is today a highly accepted risk factor for AMD and populations at risk or recently diagnosed should be encouraged to stop.

INTRODUCTION

Age-related macular degeneration (AMD) is a medical condition which results in blurred vision or central vision loss, which can make it hard to recognize faces, drive or read. This is caused by damage to the macula, and three severity grades of AMD are established: early, intermediate and late types, whilst the latter comprises “dry” AMD – non-exudative type – and “wet” AMD – exudative type (see Appendix A). AMD is not associated with visual loss early in the disease, but often progresses to retinal atrophy and central retinal degeneration – hence the name “age-related”. “Dry” AMD accounts for 90% of diagnosis, associated with a decade long visual loss as opposed to “wet” AMD, which can produce effects as rapidly as over a few months. As there is no known cure for AMD, primary and secondary prevention seem to be the best treatment options at the moment.[1–3]

Worldwide, more than 13 million people are affected by late AMD. A 0.37% prevalence is estimated, increasing with age. AMD is the most common cause of irreversible vision loss in the developed world, with an aging European and North American population being the most affected.[4] Its epidemiology is multifactorial and still subject of investigation, being clear that age, ethnicity and genetics are involved, as are modifiable risk factors such as smoking and nutrition. These are the aim of the present study, how nutrition and lifestyle influences incidence and progression of AMD. Specifically, how micronutrients such as antioxidants, carotenoids and omega-3 fatty acids and their inclusion in types of diets can help in primary and secondary prevention of AMD.

The retina is highly sensitive to reactive oxygen species. A very important line of defense against reactive oxygen species is formed by antioxidants, such as vitamin A, C and E, minerals such as zinc and selenium, and carotenoids – lutein and zeaxanthin. The latter are pigments found in dark green leafy vegetables and fruits with orange or yellow coloration, which compose the yellow pigment that protects the retina and the macula, absorbing damaging energetic blue light. Regarding studying the role of antioxidants in the retina, most research either studies their effect as a part of a diet on AMD, or the effect of administered supplements on AMD. The present study will focus primarily on non-supplemented diet and its known associations with AMD to date.

Omega-3 fatty acids, and specifically long-chain polyunsaturated fatty acids (LCPUFA) are known for its structural, functional and protective roles in the retina, such as an important anti-inflammatory function. The principal polyunsaturated fatty acids relevant in human nutrition are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA has a role in providing an adequate environment for conformational changes in rhodopsin as well as providing protection delaying apoptosis, inflammation and angiogenesis. Omega-3 fatty acids also play an important role in bilipidic membranes.

The Mediterranean diet emphasizes eating primarily plant-based foods, such as fruits and vegetables, whole grains, legumes and nuts – foods rich in antioxidants and carotenoids. Replacing butter with healthy fats, such as olive oil accounts for higher intake of omega-3 fatty acids. The Western diet, or the American diet, is precisely poorer on all these nutrients, with a high intake of processed foods and saturated fat.

It is understandable then that antioxidants, carotenoids and omega-3 fatty acids are among the micronutrients most studied for its association with AMD, individually and in the context of a specific diet.

Regarding this study's specific objectives, diverse literature exists about specific nutrients in contrast with groups of nutrients, food groups, and diets as a whole. Collecting and organizing conclusions from these studies will help to understand what has been study and what can be suggested as primary or secondary prevention to fight AMD in general. This was sought throughout the elaboration of this study as it is explained in its conclusions below.

METHODS

A systematic search was performed through the search engine Google Scholar and directly in two databases, namely PubMed and Cochrane Library.

Data sources

Search of these databases used the terms "*diet OR nutrition OR smoking OR exercise OR lifestyle OR carotenoid OR vitamin OR zinc OR lutein OR zeaxanthin AND age related macular degeneration OR macular degeneration OR age related maculopathy*". The search strategy used both keywords and MeSH terms. No limits were placed on the year of publication. References identified from bibliographies of pertinent articles or books were also retrieved.

Studies and participants

Four types of studies were gathered after searching the databases, including prospective cohort studies, cross-sectional studies, case-control studies and systematic reviews with meta-analysis. For the inclusion of studies, relevant evidence about diet, diet patterns, specific nutrients or micronutrients and their relationship with incidence and/or progression of any type of AMD was required. Studies including exclusively supplemented diet were excluded from the pool. Studies with previous diagnosis of any type of AMD were not excluded.

Outcome measures

The outcome measures were incidence or prevalence of either early AMD or late AMD, progression from healthy individuals to early or late AMD and progression from early to late AMD.

Selection of studies

The aforementioned database were searched and the abstracts of resulting articles were analyzed and excluded if lacking relevancy. Then, all the selected studies were downloaded and read in full. Studies including both evidence of diet and supplemented diet were included, and only the pertinent information was used for this review.

RESULTS

The Age Related Eye Disease Study (AREDS)

While the present study comprises specifically data and information from studies with non-supplemented diet, being that many of the included research used data from the AREDS's population, and its importance in research developments in AMD, a short introductory note to the results follows:

The AREDS is to date the most exciting piece of research on the use of antioxidants in the secondary prevention of AMD and is likely to remain the definitive study for some years to come. The results of this prospective, double-masked, multicenter, randomized clinical trial, which included 4757 participants between the ages of 55 and 80 years, were reported in a series of publications, the data pertaining to antioxidants was published in Report No. 8.[5] The key results of AREDS include a significant reduction in the probability of disease progression in patients with intermediate or advanced AMD for the subjects given antioxidants + zinc in a prepared formulation compared with those given placebo.

The AREDS2 was later attempt to assess the pertinence of inclusion of lutein and zeaxanthin supplements in the original formulation – with a rather complex study design. Nevertheless, the addition of zeaxanthin, lutein or both to the supplement formulation did not result in a further reduction in the risk of progression to advanced AMD.[6]

Description of studies

Of all the abstracts screened from the search pool, 27 studies were selected as relevant for this review. From these 27, 14 comprised prospective cohort studies[7–20], 5 cross-sectional studies[21–26], 5 case-control studies[27–30] and 3 systematic reviews[31–33] with meta-analysis.

Its results are described firstly by study type, then by group of nutrient and finally by primary or secondary prevention conclusions – and consequently by type of AMD.

Prospective cohort studies

As the name would suggest, these are studies that follow a population over a determinate period of time. As there are no randomized controlled trials about exclusively non-supplemented diet, possibly due to the complexity of their implementation, prospective cohort studies are the ones which provide more quality information when compared to plain longitudinal studies.

The lifestyle and diet patterns or nutrients that comprise the majority of these studies are smoking status[7,15], alcohol consumption[7], physical activity[15], intake of total and specific types of fat[8,16], intake of vegetables[7,17], intake of meat[7,8,16], intake of groups of food related to certain kinds of fat such as dairy products or processed baked goods[8,16], intake of fish[7,8,10], intake of lutein and zeaxanthin[9,13,17], intake of LCPUFA such as DHA and EPA[8,10,14], linoleic acid[8] and beta-carotene, vitamins C, E and zinc[17,18].

The main overall conclusions that can be summed up from this pool of prospective cohort studies (Table 1) are that increased physical activity, regular and high intake of fish and

DHA and EPA as its main reservoir, high intake of lutein and zeaxanthin, regular consumption of vegetables and nuts and antioxidants such as beta-carotenes, vitamins C, E and zinc are associated either with an decreased risk of developing early AMD, progressing from early to late AMD or preventing retinal changes such as drusen and pigmentary abnormalities. Smoking, obesity, all kinds of fats (saturated, monounsaturated, polyunsaturated and transaturated) and food groups with these, linoleic acid are inversely associated, being found as prejudicial in AMD development or progression.

Important research which comprises today's most emblematic prospective studies will be further detailed under its specific nutrient subchapter below. For example, the Rotterdam Study[18] and the Blue Mountains Study[17] regarding antioxidant effect on AMD and the 2006 POLA Study[11] on carotenoids; the 2009 SanGiovanni[14] and the 2011 Christen[10] studies on omega-3 fatty acids effects on AMD. (Table 5)

Table 1: Conclusions of the prospective cohort studies

Study	Population	Follow-up	Diet, lifestyle or nutrients studied	Conclusions
Rotterdam 2005[18]	4140 participants	8 years	Carotenes + vitamin C + vitamin E + zinc	Association with a decreased incidence of AMD
Blue Mountains 2008[17]	2454 participants	5 and 10 years	Zinc + lutein + zeaxanthin + vegetables	High zinc intake associated with decreased incidence of "dry" AMD High lutein and zeaxanthin intake associated with "wet" AMD Vegetable intake associated with decreased incidence of any AMD
POLA Study[1] *1999 2006 [10,20]*	2584 participants		Alfa-tocopherol (as precursor of vitamin E) Lutein + Zeaxanthin	Alfa-tocopherol present in high concentration in the retina and related with lower risk for AMD High levels of lutein and zeaxanthin related with decreased incidence of AMD
CAREDS 2006[13]	1787 participants	4-7 years	Lutein + Zeaxanthin Fruits + Vegetables	Only showed association with decreased incident AMD with stable intake and no comorbidities associated
Cho 2008[9]	71 494 women 41 564 men without AMD	18 years	Lutein + Zeaxanthin	No association with AMD Suggestion of high intake associated with lower late AMD risk
Cho 2001[8]	42 793 women 29 746 men without AMD	12 y. women 10 y. men	Total fat + specific fats + linoleic acid + DHA + food groups correspondent to nutrients	Total fat associated with increased incident AMD Linoleic acid and correspondent food associated with increased incident AMD DHA and fish intake associated with decreased incident AMD
Seddon 2003[16]	261 participants	4,6 years	Specific types of fat + linoleic acid + nuts + dairy products + meat + processed food	Vegetal, saturated, monounsaturated, polyunsaturated, transaturated fat and processed food associated with increased progression to late AMD Nuts associated with decreased progression to late AMD
Arnarson 2006 "Reykjavik"[7]	846 participants	5 years	Tobacco, Alcohol, Vegetables, Fish, Meat	Tobacco not related with AMD Alcohol in moderation, vegetables and fish associated with increased drusen Meat associated with decreased AMD
SanGiovanni 2009[14]	1837 from AREDS	12 years	DHA + EPA + DHA and EPA	Associated with decreased progression to late AMD
Christen 2011[10]	38 022 women without AMD	10 years	Omega-3 fatty acids + Fish	Regular consumption of DHA, EPA and fish associated with significant decreased incidence of AMD
Seddon 1996[19]	31 843 women without AMD		Tobacco	Over 25 pack-years[2] and past smokers have increased risk for incident AMD
Seddon 2003[15]	261 participants	4,6 years	Obesity + physical activity + tobacco + hypertension	Obesity, tobacco and waist circumference associated with increased progression to late AMD Physical activity associated with decreased progression to late AMD Hypertension not associated
Gopinath 2015[12]	1612 participants, 56 with AMD	10 years	Lifestyle change	Half of the participants didn't stop smoking or increased vegetable intake in their diet
Merle 2015[20]	2525 participants from AREDS	13 years	Mediterranean diet	Higher adherence to Mediterranean diet associated with reduced progression to late AMD

1: POLA Study 1999 is a case-control study but POLA Study 2006 is a prospective study, and they were included in both Table 1 and Table 2.

2: Pack-years are calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

Cross-sectional studies

This kind of study observes a specific population or representative subset at one specific point in time. Then, it is likely that the proposed outcome measure will be the prevalence of AMD, instead of progression from a healthy state to different stages of AMD.

The diet patterns and nutrients involved in this group of studies are fruits and vegetables[13], fish and shellfish[23,25], alfa-tocopherol as a vitamin E precursor[21], lutein, zeaxanthin, monounsaturated, polyunsaturated and saturated fats[24,25] and omega-3 LCPUFA[22,24,26].

What can be concluded from these studies (Table 2) is that vitamin E may be protective in AMD[21], though later studies have confirmed[18] lutein, zeaxanthin and LCPUFA to be associated as synergistic constituents of the macular pigment and to influence macular density. Fish with omega-3 fatty acids were also associated to increased risk of late AMD[23,25].

The highlights of convincing evidence with cross sectional studies will also be more deeply described in its nutrient category below. (Table 5) Regarding antioxidant relationship with AMD, the 1999 POLA Study[21] (Table 2) is the key piece of research. On omega-3 fatty acids, almost all other studies lead the research: the Reynolds 2013 and the POLANUT studies are the more important.[24,25]

Table 2: Conclusions from cross sectional studies

Study	**Population**	**Diet, lifestyle or nutrients studied**	**Conclusions**
POLA Study[1] *1999 2006 [10,20]*	2584 participants	Alfa-tocopherol (as precursor of vitamin E) Lutein + Zeaxanthin	Alfa-tocopherol present in high concentration in the retina and related with lower risk for AMD High levels of lutein and zeaxanthin related with decreased incidence of AMD
PIMAVOSA 2012[22]	107 participants without AMD	Lutein + zeaxanthin + Omega-3 LCPUFA	Macular pigment optical density associated with plasma lutein and zeaxanthin
SWENOR 2010[23]	2520 participants	Fish + seafood in omega-3 categories	Only omega-3 fish is protective against late AMD
POLANUT 2007[25]	832 from POLA study	Total, monounsaturated, polyunsaturated and saturated fat Fish	Total and monounsaturated fat associated with increased AMD Fatty fish more than once/month associated with decreased AMD
ALIENOR 2011[26]	666 participants	Omega-3 LCPUFA	LCPUFA associated with decreased early and late AMD
Reynolds 2013[24]	2531 participants from AREDS	Total, monounsaturated, polyunsaturated and saturated fat DHA + EPA + DHA and EPA Linoleic acid	High DHA intake associated with advanced AMD in Model A and Model B[2] High DHA + EPA intake associated with advanced AMD in Model B Monounsaturated fat associated with advanced AMD in Model A

1: POLA Study 1999 is a case-control study but POLA Study 2006 is a prospective study, and they were included in both Table 1 and Table 2.

2: Model A: behavioral factors (baseline AMD grade, sex, age, AREDS treatment, education, smoking, body mass index, and caloric intake); Model B: same behavioral factors and genetic variants predisposed to AMD

Case-control studies

As with cross sectional studies, case-control studies are observational because no intervention is attempted and no attempt is made to alter the course of the disease. The goal is to retrospectively determine the exposure to the risk factor of interest from each of the two groups of individuals: cases – the individuals with AMD, and controls – healthy individuals. With this kind of studies the attributable risk can also be analyzed.

The patterns which were object of study in these were smoking[34], fish, LCPUFAs and linoleic acid intake[28,34], fatty acids and fatty foods[34] and lutein and zeaxanthin.[29]

Conclusions stated (Table 3) that smokers and past smokers were at risk for AMD, with 32% of attributable risk[34] and monounsaturated, polyunsaturated, vegetable fat, linoleic acid and fatty foods intake were a deleterious risk for AMD. Fish intake, omega-3 LCPUFAs[28,34], lutein and zeaxanthin[29] were quoted as protective for AMD, results consonant with many others that can be read above.

Following the trend from the other study types groups, case-control most emblematic and convincing evidence will be further detailed in its nutrients subchapter below. (Table 5) The finest literature regarding carotenoids include the 1994 Seddon study[27] and 2007 SanGiovanni AREDS Report No.22[29]. On omega-3 fatty acids, the 2006 Seddon study[28] is an important hallmark.

Table 3: Conclusions for case-control studies

Study	**Population**	**Diet, lifestyle or nutrients studied**	**Conclusions**
Seddon 1994[27]	356 participants with advanced AMD 520 control subjects	Carotenoids + vitamins A, C, and E	Higher dietary intake of carotenoids was associated with a lower risk for AMD – lutein and zeaxanthin were most strongly associated Vitamins were not appreciably associated
Seddon 2006[28]	681 twins	Omega-3 fatty acids + linoleic acid + fish + tobacco	Smoking and past smoking associated with increased risk for AMD – 32% attributable risk Fish intake and omega-3 fatty acids associated with decreased risk for AMD
Seddon 2001[34]	349 participants with "wet" AMD + 504 healthy participants	Total, monounsaturated, polyunsaturated and saturated fat Linoleic acid + fish + omega-3 fatty acids + fatty foods	High intake of monounsaturated, polyunsaturated, vegetal fat, linoleic acid and fatty foods associated with increased AMD Fish and omega-3 intake associated with decreased AMD
SanGiovanni 2007 (AREDS Report No. 22) [29]	4519 participants from AREDS	Lutein + zeaxanthin	Lutein and zeaxanthin intake associated with decreased AMD
Chiu 2014[30]	4088 participants from AREDS	Oriental diet pattern: higher intake of vegetables, legumes, fruit, cereals, tomatoes and seafood Western diet pattern: higher intake of red and processed meat, dairy products, French fries and eggs	Oriental diet associated with decreased AMD Western diet associated with increased AMD

Systematic reviews with meta-analysis

This type of studies, are in part similar to the present one. However, by including meta-analysis, instead of each study analyzing every nutrient, different studies focused on individual nutrients. Then, including systematic reviews with meta-analysis in this research has great pertinence: we can start to identify a pattern in the results from all the different types of studies mentioned above and eventually foresee the conclusions gathered in these reviews.

Following there is a sum of what the three systematic reviews have concluded. Further below in the study, more relevant information can be encountered in context with its nutrient or AMD type subchapter. (Table 5)

The first, by Chong in 2007 states that with the current scientific evidence, vitamin A, vitamin C, vitamin E, zinc, lutein, zeaxanthin, α carotene, β carotene, β kryptoxanthin, and lycopene have little or no effect on early AMD. It is worthy of mentioning that this specific study only includes primary prevention on its scope, meaning that the search and analysis was about studies that find the association of nutrients with incidence of AMD.[31]

On another hand, Chong 2008 concludes that high dietary intakes of omega-3 fatty acids and fish are associated with a reduced risk of both early and late AMD. However, it is stated that due to the small amount of literature available on the subject (as of 2007) and absence of any randomized controlled trials no dietary recommendation can be made.[33] As of 2015, at the date of writing of this article, there are considerably more literature on the matter which could supposedly alter these conclusions.

Last but not least, the last systematic review – Ma 2012 - includes exclusively lutein and zeaxanthin and draws interesting conclusions, being that both these carotenoids are

protectively associated with progression to late AMD but not with risk of incident early AMD[32] concordant conclusion with Chong 2006.

Table 4: Conclusions for systematic reviews and meta-analysis studies

Study	**Conclusions**
Chong 2007 [31]	Little evidence yet that micronutrition plays an important role in primary prevention – incidence – of AMD
Chong 2008[33]	Studies point to the same protective association of antioxidants and carotenes and AMD, although still little evidence regarding omega-3 LCPUFA
Ma 2012[32]	Lutein and zeaxanthin protectively associated to secondary prevention – progression to late AMD – but not associated to primary prevention – incident AMD.

Description by diet, lifestyle or nutrients studied

Below are presented the main studies' conclusions organized by group of nutrients. The most emblematic and game-changing pieces of literature are detailed along as well. Table 5 identifies precisely these aforementioned studies.

Table 5: Emblematic studies on each specific group of nutrients.

Group	**Emblematic studies**
Smoking	1996 Seddon[19]
Antioxidants	1999 POLA Study[21] 2005 Rotterdam Study[18] 2008 Blue Mountains Study[17]
Lutein and zeaxanthin	1994 Seddon study[27] 2006 POLA Study[11] 2007 SanGiovanni AREDS Report No.22[29] 2008 Blue Mountains Study[17]
Fish and LCPUFA	2006 Seddon study [28] 2007 POLANUT[25] 2009 SanGiovanni[14] 2011 Christen[10] 2013 Reynolds[24]
Whole Diets	2014 Chiu[30] 2015 Merle[20]

Physical activity

There is very few research conducted regarding physical activity, possibly due to the most adequate method to acquire this data being self-reported, which is susceptible to bias and not very reliable. However, in the only study found, physical activity was associated with reduced risk of progression to AMD. Moreover, it is widely known and proven that physical activity decreased cardiovascular risk and that it is associated with healthier lifestyle. Then so we can infer that physical activity is indirectly a protective factor for AMD, because it is associated with a lower intake of fats and fatty foods and higher intake of vegetables, fruit and for that matter antioxidants and vitamins.[15]

Smoking

The pioneer in studying tobacco associations was the 1996 Seddon study. It was a large prospective study that involved the biannual follow-up during 12 years of over 30 000 women from the Nurses' Health Study from the United States. Resulting 556 338 person-years of follow-up, 215 women were diagnosed with AMD. After adjusting for other risk factors for AMD, such as body mass index (BMI), hypertension, high cholesterol, alcohol and carotene intake among others, women who currently smoked 25 or more cigarettes per day were 2.4 times more at risk of developing AMD than never smokers. Past smokers of the same amount had also 2 times the risk of AMD relatively to women that never smoked. Also, compared with current smokers, a little reduction in risk of AMD was suggested even in participants that had quit smoking for 15 or more years. The risk of AMD increased too with an increasing number of pack-years smoked (P for trend <.001). Analyses of dry and exudative types of AMD revealed no difference of results between them.[19]

The large population, prospective design and strong dose relationship tobacco-AMD made this study today's hallmark in evidence that tobacco is prejudicial in AMD development and an established risk factor. As of 2007, cigarette smoking remained the only widely accepted modifiable risk factor for the primary prevention of AMD.[31]

However, there is a 2015 study suggesting that lifestyle changes in AMD diagnosed patients are not being accepted, such that half of the patients in this study haven't stopped smoking or improved their diet.[12] This study has a potential lack of power to detect associations due to few incident AMD cases, albeit the type of data is unique in this field of study.

Smoking not only increases oxidative stress but also increases inflammatory responses, and both of these mechanisms are associated with AMD. Age-related macular

degeneration is a common eye disease in older persons, smoking is a common avoidable behavior, and dietary habits are modifiable; therefore, a proportion of visual impairment and blindness due to AMD could be prevented with attention to healthy lifestyles.[28]

Antioxidants: beta-carotenes, vitamins C, E and zinc

Oxidative stress is hypothesized to be one of the pathogenic mechanisms in AMD. The retina is thought to be highly susceptible to oxidative stress given its high oxygen consumption, high concentration of polyunsaturated fatty acids and photosensitizers, and exposure to light. Thus, it seems plausible that antioxidants may interfere beneficially in the pathophysiology of AMD. Also, zinc is concentrated in the retina and is a cofactor for many enzymes, including the antioxidant enzymes superoxide dismutase and catalase that are present in human retinal pigment epithelium.

Pathologies Oculaires Liées à l'Age (Age-related Ocular Diseases) or commonly designated the POLA study is a 1999 population based cross-sectional study, and one of the first to relate antioxidants with AMD by studying its plasma levels. It was carried out in 2584 habitants of a French city, *Sète*. Its results concern the level of alpha-tocopherol and how it relates to AMD. Alpha-tocopherol is the form of vitamin E preferentially absorbed and stored in humans. However, the plasma level of this compound should be expressed in terms of concentration within lipids of lipoproteins to avoid biases, which was shown by the absence of statistical significance in non-lipid standardized alpha-tocopherol levels results. The POLA study shows that the prevalence of late AMD was decreased by 82% in the highest quintile of the alpha-tocopherol–lipid ratio (P=.003) – a certainly strong association. Also, high levels of the alpha-tocopherol–lipid ratio were also associated with a decreased incidence of early signs of AMD. Since this study is cross-sectional, we cannot assume that low alpha-tocopherol levels preceded the development of AMD. There is a possibility that participants with late AMD have

modified their diet after developing visual impairment because of difficulties with daily life. Nevertheless, the fact that a similar association with the early, asymptomatic signs of the disease was observed, is in favor of a true “causal” relationship.[21] This can only be further confirmed with prospective studies such as the ones right below.

The Rotterdam study is a 2005 prospective study evaluating the influence of dietary antioxidants in incident AMD, namely vitamins C, E and zinc. It started with a pool of 5836 participants at risk for AMD and finished with 4170 at the final 8-year average follow-up. After this time, 560 participants developed AMD. As a result, dietary intake of both vitamin E and zinc was inversely associated with incident AMD. More importantly, an above-median intake of the combination of vitamins C and E, beta carotene, and zinc was associated with a 35% lower risk of incident AMD. This seems to corroborate the previous study in stating that vitamin E is a protective factor to AMD and adds that also the other antioxidants are too. The data was collected through a food frequency questionnaire, which wasn’t validated for all nutrients, such as vitamin E. However, for the remaining validity was shown to be moderate to good. This study suggests that the risk of AMD can be modified by diet, in particular by dietary vitamin E and zinc.[18]

Once again, although the present study does not verse on supplemented diet, the AREDS study, introduced above as a big randomized controlled trial in which participants already had a diagnosis of AMD, showed that the ones with a high intake of these 4 antioxidants had an approximately 25% reduced risk of progression from relatively advanced early AMD stages to late AMD.[5]

However, the early 1994 Seddon study[27] could not statistically confirm the same strong protective association of antioxidants regarding AMD.

The 2008 Blue Mountains Study, prospective cohort, found that high intake of zinc made it less likely of any incident AMD while vitamin E was suggestively associated with risk for late AMD. However, it could not confirm the protective effect association of antioxidants and beta-carotenes combined, such as in the Rotterdam study or with the AREDS combinations. These results suggest a possible threshold effect of total zinc intake on risk of early or any AMD, meaning that there might be a protective effect from high intakes of zinc.[17] More detail on this study can be found on the next subchapter regarding lutein and zeaxanthin.

A higher intake of vitamin E can be achieved by consumption of whole grains, vegetable oil, eggs, and nuts. High concentrations of zinc can be found in meat, poultry, fish, whole grains, and dairy products. Carrots, kale, and spinach are the main suppliers of beta carotene, while vitamin C is found in citrus fruits and juices, green peppers, broccoli, and potatoes.

Lutein and zeaxanthin

These carotenoids, often referred as xanthophyll, are two abundant substances of the macula. The carotenoids are thought to function as antioxidants and/or as a blue light filter, to protect the underlying tissues from phototoxic damage. Several studies, as seen above, have associated lutein and zeaxanthin with AMD. These carotenoids are traditionally found in green vegetables.

The Eye Disease Case-Control Study Group was the first evidence to suggestively tie carotenoids with AMD.[35] Shortly after, the 1994 Seddon study followed. Using the same case-control design, 356 cases with diagnosed AMD and 520 healthy controls from five ophthalmology centers in the United States participated. The results, adjusting for other risk factors for AMD, such as smoking status, alcohol intake, BMI, blood pressure

and self-reported physical activity, found that those in the highest quintile of carotenoid intake had a 43% lower risk for AMD compared with those in the lowest quintile. Moreover, lutein and zeaxanthin were the most strongly associated with AMD[27] – this was the first time that these two specific carotenes were associated with AMD, which gave way to more directed studies along the years. The PIMAVOSA 2012 study connected macular density with the plasma level of lutein and zeaxanthin.[22]

The 2006 POLA study is a cross-sectional study from the same population as the original one[21]. Among the original participants from the French city of *Sète*, 899 participated. This time, it was designed to assess plasma carotenoids, namely lutein and zeaxanthin. Plasma lutein and zeaxanthin showed a strong inverse association with AMD – 79% reduced risk comparing high versus low plasma levels. The association with plasma zeaxanthin was particularly strong, with participants with highest levels having 93% reduced risk compared to the lowest levels. Other carotenes studied did not show statistically significant association. Adjustments for AMD risk factors, such as smoking, high density lipoprotein (HDL) cholesterol levels and BMI did not affect the results. As there were little cases of late AMD, the statistical analysis was with all types pooled together – from what we can conclude that these associations concern mainly early AMD.[11]

The 2007 SanGiovanni AREDS Report No.22 is a case-control study with 4519 participants, in which 1115 are controls. Its objective was to evaluate the relationship between dietary carotenoids with prevalent age-related macular degeneration in context of the AREDS study population. To pursue this goal, food frequency questionnaires were completed by the participants, which reported the data by nutrient intake values. These were then adjusted for total energy intake prior to analysis. The most important results stated that study participants reporting the highest dietary intake of lutein/zeaxanthin were

statistically less likely to have advanced AMD or large or extensive intermediate drusen than those reporting lowest dietary intake.[29] For what can be extracted from this study, we can say that it comes as a complementary evidence to the POLA study above – lutein and zeaxanthin affect advanced AMD as well.

The 2008 Blue Mountains Study is a prospective cohort study designed to assess the relationship between dietary antioxidants and carotenoids and the risk of AMD. With number of participants as large as 2454, follow-up took place after 5 years, 10 years, or both. Results on antioxidants were already approached above, but on carotenes, the higher tertile of dietary lutein and zeaxanthin intake had a reduced risk of incident neovascular AMD, and those with above-median intakes had a reduced risk of incident indistinct soft or reticular drusen. This is further supported by the finding that those also in the highest tertile of vegetable intake, compared with the remaining population, were less likely to develop any AMD.[17] This is another solid evidence that lutein and zeaxanthin are the two carotenes most closely related with not only advanced AMD but also early AMD.

But can these nutrients be found only in green vegetables?

It has been suggested that leafy green vegetables, such as spinach, celery, Brussels sprouts and broccoli, are good sources of these carotenoids. However, it was found that although these are good sources of lutein, their composition in zeaxanthin was very low. Lutein also was also the major carotenoid in kiwi fruit, red seedless grapes, zucchini squash, and pumpkin. Zeaxanthin was the major carotenoid in orange pepper, which was also the food with the highest percentage of this carotenoid among all fruits and vegetables evaluated in this study. The highest mole percentage of both lutein and zeaxanthin was found in egg yolk. Since eggs have a high cholesterol content, a restricted intake of eggs has been recommended for many years, since cholesterol is a risk factor for coronary artery disease. However, in recent years several studies were published showing that a higher intake of

cholesterol through the addition of more eggs in the diet, results not only in an increase of serum cholesterol, but also in an increase of HDL cholesterol. Since HDL cholesterol is protective against atherosclerosis, extra egg consumption may not change the risk index for ischemic heart disease based on the cholesterol levels. The consumption of eggs could actually be beneficial in order to obtain a higher intake of lutein and zeaxanthin, and since it has no severe adverse effects on cardiac risk factors, the exclusion of eggs from the diet could be reconsidered.[36]

Also, as mentioned above, and though is outside the scope of the present study, the AREDS2 randomized controlled trial hypothesized if lutein and zeaxanthin would improve the risk reduction in AMD patients in addition to the previous antioxidant supplement formulation from the AREDS original study. However, it was not shown a statistically significant overall effect on progression to advanced AMD or changes in visual acuity in patients with previously diagnosed AMD.[6] Nevertheless, and regarding the above results displayed, even if lutein and zeaxanthin supplementation do not have a positive effect on AMD, it's dietary intake and intake bound to fruits and vegetables is proven to have a protective effect on any type of AMD.

Fruits and vegetables, as seen above, are a natural source of dietary carotenoids and antioxidants. Long have been the recommendations and studies about the benefices of this food group in all kinds of major disease groups, such as cardiovascular diseases and cancer. Most of the studies that include micronutrients existent in fruits and vegetables also analyze the association of AMD with this food group, so we can be more certain of the provenience of these nutrients and that their effect is as protective as a nutrient or as part of a food group.

Fish and LCPUFA

Fatty acids may be divided into 3 types: saturated fat from dairy products and meat, monounsaturated fatty acids (MUFA) from olive oil, and polyunsaturated fatty acids (PUFA). Omega-3 fatty acids are essential to the human being, meaning that they are not synthetized by the body. Fish and seafood are a known reservoir of omega-3 LCPUFA and they may help lower the risk of heart disease, depression, dementia, and arthritis. Long chain omega-3 fatty acids (LCPUFA) – especially EPA and DHA – have different roles in the retina as mentioned in the introduction of the present study: there is a morphological role, as DHA is the major structural lipid (80%) of retinal photoreceptor membranes; a functional role, because DHA provides an adequate environment for conformational changes in rhodopsin and finally a protective role, as EPA and DHA have anti-apoptotic, anti-inflammatory and antiangiogenic functions that protect against aging of the retina and may reduce lipofuscin accumulation in the retinal pigment epithelium and lipid deposit in Bruch's membrane. Alongside this, the PIMAVOSA study associated the macular density with levels of DHA and EPA.[22]

In light of AMD presumed pathophisyology, LCPUFA may have a special role in the function of the retina in addition to above mentioned. Rod outer segments of vertebrate retinas have a high DHA content. However, photoreceptor outer segments are constantly being renewed; therefore, a constant supply of these fatty acids is required and marginal depletion of these fatty acids might impair retinal function and influence the development of degenerative diseases such as AMD.[8] Because of the plethora of roles omega-3 LCPUFA have in the retina, there is biological plausibility of a relationship between the intake of omega-3 fatty acids and the progression of AMD[16], which we will find out by the several studies below.

The 2006 Seddon study[28] is a case-control study designed to identify modifiable risk factors, such as smoking, fish intake and omega-3 fatty acids intake for AMD. The population consisted on 681 elderly male twins from the National Academy of Sciences–National Research Council World War II Veteran Twin Registry, 222 of which with intermediate or late AMD and 459 healthy or with early signs. Risk for AMD according to cigarette smoking and dietary fat intake was estimated using logistic regression analyses. The results stated that increased intake of fish reduced risk of AMD, particularly for 2 or more servings per week. Also, dietary omega-3 fatty intake was inversely associated with AMD comparing the highest and lowest quartile. What's more, reduction in risk of AMD with higher intake of omega-3 fatty acids was observed among subjects with below-median levels of linoleic acid intake, an omega-6 fatty acid. This agrees with the need of maintaining a healthy balance between omega-3 and omega-6 fatty acids. This imbalance is attributed to a diet rich in processed foods containing or cooked in vegetable oils, which a study by the same author has previously shown to increase the risk of AMD[16]. About a fifth of the cases were estimated as preventable with higher fish and omega-3 intake.

In the Seddon 2003 study, results also show that consumption of transunsaturated fatty acids increases the risk of AMD and its progression. Metabolic studies have shown that transunsaturated fats have adverse effects on blood lipid levels by increasing low-density lipoprotein cholesterol while decreasing high-density lipoprotein levels, and this effect can be twice that of saturated fatty acids. Transunsaturated fats are also known to be associated with an increased risk of coronary heart disease.[16] Regarding fatty acids and linoleic acid several other studies showed association between total, vegetal, monounsaturated, and transunsaturated fat and increased risk for AMD. Linoleic acid was

also found as prejudicial, however there is yet no explanation for its physiological mechanism of acting in AMD.[8,16,25,34]

The 2007 POLANUT study is a cross-sectional study designed to evaluate dietary fat and the risk of AMD. The population was the original one from the POLA study, however only 832 survivors participated. Nutritional data was collected from a food frequency questionnaire. Results stated the following: after adjustment for age and gender, risk of AMD was increased in subjects with high intake of total and monounsaturated fat and tended to be increased in those with high saturated fat intake. Total PUFA intake was not significantly associated with AMD, not even adjusted for risk factors. Concerning fish intake, total fish intake was not significantly associated with AMD. The risk for AMD was reduced in subjects consuming fatty fish more than once a month.[25] Although conclusions are not agreed with the trend of fish and PUFA being protective for AMD, this study proves instead the deleterious effect of monounsaturated and saturated fat.

The 2009 SanGiovanni is a prospective cohort study which was undertook within the AREDS, aiming to investigate whether omega-3 LCPUFA influenced the development of late AMD. With a population of 1837 participants with established diagnosis of AMD, a food frequency questionnaire and an annual follow-up for 12 years was employed. After this time period, 364 people progressed to central geographic atrophy (CGA) and 583 progressed to neovascular (NV) AMD, both forms of late AMD. Results pointed that participants who reported the highest intake of omega-3 LCPUFAs – namely DHA, EPA or both – were 30% less likely to develop late AMD than were the ones reporting the lowest levels of intake of omega-3 LCPUFAs.[14] This is yet another study which follows the trend of proof that LCPUFA have in fact a protective relationship with AMD, specifically late AMD. This particular study does not independently evaluate fish intake as the LCPUFA main source.

The 2011 Christen study, yet another prospective cohort, had yet again the objective of analyzing the incident AMD with the intake of omega-3 LCPUFA and fish. A total of 38022 women from the Women Health Study completed a food frequency questionnaire and were free of a diagnosis of AMD, and during the 10 average years of follow-up, 235 cases of incident AMD were reported. Resulting from the research, women in the highest tertile of intake for DHA and EPA compared to those in the lowest, had a significant decreased risk of AMD. Consistent with the findings for DHA and EPA, women who consumed 1 or more servings of fish per week, compared to those who consumed less than 1 serving per month, had a 42% decreased risk of AMD.[10] There we have then another evidence supportive of omega-3 and fish intake being protective, particularly, of early AMD.

The Reynolds 2013 study is one of the most recent studies in AMD and consists on an observational analysis of a prospective cohort, or a cross sectional study set in context of the AREDS. Among the participants, 2531 individuals from the Age-Related Eye Disease Study, 525 eyes progressed to geographic atrophy (GA) and 4165 eyes did not. This study did an interesting approach, dividing adjustment calculations from the food frequency questionnaires data in two models, “model A” including behavioral factors, such as baseline AMD grade, sex, age, AREDS treatment, education, smoking, BMI, and caloric intake, and “model B” adding up genetic predisposing variants. Summing up conclusions, the high intake of LCPUFA was considered as inversely associated with AMD (GA and early and late AMD) in “model B” population. In addition, monounsaturated fats were associated with increased risk for AMD in the “model A” population. Finally, and curiously, high DHA intake was associated with a risk genotype for AMD but was not associated with non-risk genotypes, meaning that nutrients may have influence in genetic predisposition, which warrants further study.[24]

In general, there have been several studies that point out that LCPUFAs and fish intake as its source is protective either for any incident AMD or progression to worse stages in populations that have been already diagnosed. Nevertheless, it is very important to stress that the ratio between omega-6, which is present in vegetable oils mainly, and omega-3 is determinant in the protective effect of the latter fatty acids towards AMD. Beyond vegetable fat, also monounsaturated, polyunsaturated, and transunsaturated fat are related with increased risk for AMD and thereby should be avoided.

Diet patterns

Although there are some solid conclusions already that point out protective effect of antioxidants, carotenes and omega-3 fatty acids on AMD, do these effects replicate in context of a complete diet pattern, were all nutrients and foods have complex interactions and are processed by the body? This is a reason why more recently, new research is being targeted to diet patterns rather than individual nutrients. In contrast to the traditional analytic approach relating single nutrients or foods to disease risk, dietary pattern analysis considers overall diet and thus would more closely relate to and inform about the effects of actual eating patterns on risk for AMD.

The Chiu case-control study from 2014, took on an original perspective and instead of picking specific nutrients or groups of food, divided first the diet of their population of 4088 participants from AREDS study in two patterns, the first “healthy” diet with more vegetables, fruits and cereals intake, and the second “unhealthy” diet with high intake of red and processed meat, dairy products, French fries and eggs. The results produced a decreased risk for AMD with the first “healthy” diet and an increased risk with the second “unhealthy” diet. Plenty of nutrients in all other studies considered in this review that were either protective or of lower risk to AMD are included in the “healthy diet” and conversely for the “unhealthy” one.[30] It is important to note that these findings are

consistent with associations between AMD risk and intakes of nutrients or foods identified in previous epidemiologic studies shown throughout this study.

Merle, in 2015 produced a new prospective cohort study worth highlighting. Data was collected once again with a food frequency questionnaire and the alternate Mediterranean diet score was constructed from individual intakes of vegetables, fruit, legumes, whole grains, nuts, fish, red and processed meats, alcohol, and the ratio of monounsaturated to saturated fats. The study concluded from 2525 subjects from the AREDS study that a higher adherence to a Mediterranean-type diet – represented by a high score – is linked to decreased progression to late AMD.[20] This represents a new approach to nutrition and AMD, and although no study has yet investigated the detailed mechanisms by which different dietary patterns have reduced or increased the likelihood of early or advanced AMD. However, the mechanisms must be the result of the complex interactions among different foods and nutrients in diet. A randomized controlled feeding trial that tests biomarkers for postulated mechanisms, such as advanced glycation end-products formation, oxidative stress, inflammatory responses, angiogenesis, and so forth, could be helpful to determine the mechanisms.

Description by type of AMD

Finally, the collected data is displayed according to the type of AMD (Table 6), more exactly the influence in incident early AMD or progression to late AMD and how it concerns primary and secondary prevention respectively.

Table 6: Distribution of studies according to type of AMD

Type of AMD in study	Study	Group of nutrient
Early AMD	Reykjavik 2006[7], Blue Mountains 2008[17]	Antioxidants
	Cho 2008[9]	Lutein and Zeaxanthin
	Christen 2011[10]	Fish and Omega-3 LCPUFA
Early and late AMD	POLA Study 1999[21], Rotterdam 2005[18]	Antioxidants
	POLA Study 2006[11], CAREDS 2006[1][13]	Lutein and Zeaxanthin
	Cho 2001[8], Seddon 2006[28], POLANUT 2007[25], Alienor 2011[26]	Fish and Omega-3 LCPUFA
	Chiu 2014[30]	Diet patterns
Late AMD	Cho 2008[9]	Antioxidants
	SanGiovanni AREDS Report 2007[29], Blue Mountains 2008[17]	Lutein and Zeaxanthin
	Seddon 2001[34], Swenor 2010[23],	Fish and Omega-3 LCPUFA
Progression to late AMD[2]	Seddon 2003[16], SanGiovanni 2009[14], Reynolds 2013[24], Merle 2015 [20]	

1: The CAREDS 2006 study analyzed incidence of intermediate AMD.
2: The correspondent studies analyzed not incidence but progression from AMD to late AMD.

Although the table above indicates several studies as representative of both types of AMD, their conclusions and results were in some cases just associated with one of the types, as it can be understood below.

Regarding the consumption of tobacco, several studies have been described above and its deleterious effects regard all types of AMD, and therefore it will not be detailed further below.

Diet, lifestyle and early AMD

Regarding specific results of studies concerning to primary prevention or associations with incident AMD, mainly early AMD, in a big prospective study by Cho 2008 no association was found between intake of lutein and zeaxanthin and early AMD, not even across cohorts, subtypes of AMD, and smoking status, intakes of vitamins C and E, and BMI.[9] It was suggested that each of these carotenoids may have an independent role not yet fully understood regarding early AMD. However, in the 2006 POLA study, high plasma lutein and zeaxanthin were associated with a reduced risk of all types of AMD.[11] Nevertheless, there were several limitations on this study, such as characteristics of the population, which was under representative of older people and over representative of wealthier classes.

On this particular study, the 2006 Reykjavik study, an effect of increasing incidence of early AMD was found in alcohol drinkers. On another hand, higher intake of fiber rich vegetables increased risk for drusen development. Moreover, decreased intake of meat but high intake of herring found as protective for early AMD.[7] This study has particular limitations: firstly, it has a very high volume of calculations which may result in false relationships according to the probability theory. Secondly, this is a study based on an Iceland population, and although the AMD phenotypes are the same as in the US and remaining Europe, the lifestyle and diet patterns in that country (such as the high fish intake) may twist the results.

In this Cho 2001 study, high total fat intake increased risk of incident AMD, risk which was attenuated when adjusted for linoleic acid and transunsaturated fat. Then, food groups high in linoleic acid and transunsaturated fat were analyzed and found to be of higher risk to incident AMD.[8] This could mean that, besides fat being prejudicial, there are these specific fats that are more closely related to early AMD prejudice. This could be important

for diet recommendations, taking into account the negative relationship between these kinds of fats and cardiovascular disease.

In the same study mentioned above, DHA intake and fish as its source were found to have a protective association with AMD.[8] On another publication, the Alienor 2011 study, a strong inverse association of early AMD with omega-3 LCPUFA's was found.[26] An important detail is that these results were adjusted for the major genetic polymorphisms associated with AMD. Moreover, in the Christen 2011, a big 10 year prospective study, regular intake of LCPUFAs and fish decreased risk of incident AMD, conclusions which reinforce strength in the role of these kind of "good fats" in AMD pathogenesis.[10] And finally, in the Seddon 2006 study, smoking was found to increase risk while once more, fish consumption and omega-3 fatty acid intake reduce risk of AMD.[28]

In the Rotterdam study already mentioned, a high dietary intake of beta carotene, vitamins C and E, and zinc was associated with a substantially reduced risk of incident AMD in elderly persons.[18] This study states very important conclusions, suggesting that the risk of AMD can be modified by dietary habits, and more meaningful the intake of foods rich in these nutrients appear to be more important than nutritional supplements. Regarding the Blue Mountains study, high zinc and vegetable intake were associated with lower risk of incident early AMD.[17] Also, in this study, beta-carotene were controversially associated with prejudice to AMD, although no biological explanation for this finding was proposed.

In the already mentioned Chiu 2014 study, the oriental type diet (the "healthy" diet), classified according to higher intake of vegetables, legumes, fruit, whole grains, tomatoes, seafood, and so forth was associated with reduced risk for all AMD types, including early AMD.[30]

Diet, lifestyle and late AMD

Considering now results specific for incident or progression to late or neovascular (NV) AMD, one prospective study by Cho in 2008, found a non-statistically significant suggestive association between intake of lutein and zeaxanthin and late AMD among never smokers but not across age groups, intakes of vitamins C and E, and BMI.[9] It also suggested that independently studying these carotenoids might shed some light on its contribution to neovascular AMD.

Another study, the SanGiovanni AREDS Report from 2007, associated a higher intake of lutein and zeaxanthin from foods to have a reduced likelihood of developing NV AMD.[29] A big particular strength of this study is the large sample from de AREDS population.

This particular study, the CAREDS 2006, with population from the AREDS study, was the only study that included results for incidence of intermediate AMD which was decided for inclusion in the late AMD reports conclusions. Then, it was concluded diets rich in lutein plus zeaxanthin may protect against intermediate AMD in healthy women younger than 75 years.[13] Women older than this age had no association with AMD, possibly because if they are still alive, they have more probability of having had a healthier diet than the people in their birth cohort that are already deceased.

Results of the Blue Mountains study, again, stated that high zinc, lutein and zeaxanthin and vegetables intake were associated with lower risk of incident late AMD.[17] Noticeable is that vegetable protective association with AMD further supports lutein and zeaxanthin association. These are consonant with the various studies above, which can probably lead us to recommend lutein and zeaxanthin, in their mainly form as vegetables, to patients at risk for progressing or developing late AMD.

Regarding fatty acids, there are also a few concordant studies. Firstly, in a Seddon 2003 study with results controlled for BMI; total fat, vegetable fat, saturated, monounsaturated, polyunsaturated, and transunsaturated fats and baked goods were associated with a higher risk of progression to late AMD.[16] In another study from the same author and following the trend, higher intake of vegetable, monounsaturated, polyunsaturated fats were associated with higher risk for late AMD.[34] Lastly, in a relatively newer study, the POLANUT 2007, increased risk of AMD was found as consistent with subjects with high fat, and in particular high MUFA, intake.[25] However, in this last study there was a low statistical power, nonetheless the conclusions are congruous with the remaining. It should be fair to recommend careful fat intake in AMD vulnerable populations, thinking that fat adds to an inflammatory state and could be connected with AMD pathophysiology.

In the Swenor 2010 study regarding fish, seafood and/or shellfish consumption, a protective effect of fish and shellfish intake against the risk of advanced AMD was found, most likely because of their omega-3 fatty acid content.[23] Also in the Seddon 2003 study presented above regarding fatty acids, also higher fish intake and nut intake were protective.[16] In the POLANUT cross sectional study again, the risk for AMD was reduced in subjects consuming fatty fish more than once a month.[25] And last but not least, fish and seafood were the main sources of LCPUFA's in the SanGiovanni 2009 study and this concludes that if the results are further confirmed by other studies or clinical trials, simple recommendations can be made to prevent progression to late AMD.[14]

The SanGiovanni 2009 study was a 12-year prospective cohort in which those reporting that higher intake of omega-3 LCPUFA's were associated with a lower risk for CGA and NV AMD, late AMD.[14] In the Alienor 2011 study also inverse associations of neovascular AMD with omega-3 LCPUFA's were found.[26] Two case control studies

also stated the following: there is evidence of a protective relationship with omega-3 fatty acids and fish, in the Seddon 2001 study[34]; and smoking increases risk while fish consumption and omega-3 fatty acids intake reduce risk of AMD – Seddon 2006.[28] The Reynolds 2013 study found that increased self-reported dietary intake of omega-3 fatty acids is associated with reduced risk of GA and may modify genetic susceptibility for progression to GA, as already detailed above.[24] Recommending fish and omega-3 LCPUFA's intake as its source seems to be a safe bet, accounting for the high number of studies on this specific nutrients and their protective effects on progression or incidence of late AMD.

Regarding lifestyle and other non-diet related factor, only the Seddon 2003 study presented the following conclusions: BMI over 25, high waist circumference and high waist-hip ratio turned out to increase the risk of progression to late AMD. Physical activity reduced rate of progression.[15] It seems likely that obesity is related with fat intake and more prejudicial diet and lifestyle. Conversely, higher physical activity presupposes exactly the opposite. That said, and with the current knowledge regarding its effects on cardiovascular, oncologic diseases and life expectancy itself, a normal BMI and high physical activity are also good recommendations for lower AMD risk, or even progression or incidence of late AMD.

In the newest study of this review, the Merle 2015 study, it was concluded that higher adherence to a Mediterranean-type diet is associated with a 26% reduced risk of progression to advanced AMD.[20] The protective association of the Mediterranean diet with AMD progression was driven by the fish and vegetable components, the main sources of omega-3 LCPUFAs, lutein, and zeaxanthin. However, the association was stronger from the diet as whole than individual nutrients. This further supports the trend

of new whole diet oriented studies with the premise that nutrients are not eaten isolated and its interactions may provide even greater protective effect when in context of a diet.

DISCUSSION

Strengths and weaknesses of the studies

Strengths of this pool of studies include some large cohorts, a big variety of nutrients, diet patterns and lifestyle aspects. Analysis of the influence or association of these with both types of AMD is also a point in favor. And, in general, the complementary literature review in the discussion part of these articles provided a fairly good understanding on how the particular nutrient or aspect has been studied and how did those results compared with the already available.

There were no randomized controlled trials found in this research, and although most prospective cohort studies had extensive analysis, in smaller articles not all were non-evaluative of early and late AMD independently.

In almost all the studies, there was a possible bias due to the representation of the population. Either they were big samples of health care professionals and therefore more health conscious, or older groups from well-nourished United States or Western European populations and even small samples unrepresentative of specific populations. There was not a single international multicenter study that englobed all social and financial statuses.

In some of the studies, the method of AMD assessment and diagnosis was only by reduced visual acuity which contrast with articles that made this diagnosis by optical photography. This may suggest that studies that used only visual acuity tests have less cases of diagnosed AMD for testing.

As it certainly is and has been very important to show the role of each individual nutrient and its definite association with AMD, it is important to notice that new studies have analyzed diet patterns as a whole. Evidently there is some sense in this, as nutrients are not ingested alone but as part of a certain food and interact with each other after digestion,

having possibly a synergistic effect. That said, it shall be of importance to study various world diets and improve the recommendations for AMD prevention from "eat vitamin E and vegetables" to "eat a Mediterranean diet" as such.

Finally, a vast majority of the articles used food frequency questionnaires, more or less elaborated and some recalling diet patterns from 3 or more years before. A "time bias" is possible to have occurred then.

Limitations of this study

The present literature has some important limitations. Firstly, it is merely a literature review. The work simply consisted of database search and observational analysis of which nutrient, what kind of population and what kind of analysis had been performed. The results were a mashup of all study results, discussion and conclusions. No meta-analysis was performed so no statistical results are presented. No heterogeneity tests, sensitivity analysis or publication bias tests were performed either. However, there was an important division of data analysis that was made: firstly, literature was approached from each type of study that has a certain amount of importance and power inherent to it; secondly, the information was split according to the three major groups of nutrients that have relationship with the disease; and lastly, according to the outcome measure of studies – if related to incident AMD or progression to later stages of AMD, representing either primary or secondary prevention.

Suggestions for the future

Recommendations of what can be further done on diet and AMD research are in order. For starters, more and bigger prospective cohort studies are necessary. Regarding that some very strong evidence of the protective effects of specific nutrients is now

increasingly convincing, studies that evaluate complete diets instead would be more likeable and acceptable for recommendations in AMD prevention.

On another hand, randomized controlled trials focused on primary prevention would be the strongest affirmation on the relationship with AMD. However, the study method could become somewhat unethical if based purely on diets – one could not have a control group eating an unhealthy diet with all the proven prejudices on the cardiovascular system among others, and a study group with a healthier diet just for the sake of AMD prevention. That being said, more supplemented trials in healthy individuals seem to be the best option to emulate a healthier diet. Those conjoined with the remaining prospective cohort evidence could finally bring firm solid certainties on AMD's modifiable factors.

Last but not least, it is true that AMD is the disease of developed countries and its aging populations. However, most studied populations represent groups of higher economic status, which may bias some conclusions regarding the matter, being that these may have easier access to health care, may be more aware health-wise among others. It is urging then to have studies which are more representative of a broader scope of the developed countries population.

CONCLUSION

As it has been proven in the AREDS randomized trial that beta-carotene, vitamin C, E and zinc supplements were found to be protective for AMD progression, various big prospective studies have proven that the same dietary nutrients are protective to incident early AMD, and food groups with these nutrients should be recommended.

Regarding lutein and zeaxanthin, plenty of evidence has been provided that, being important components of the retina, these carotenes and more importantly, vegetables and fruits, exercise a protective effect on AMD and thereby it could be recommended.

Omega 3 LCPUFAs were proven as protective to AMD at many instances in the last years and although no specific meta-analysis has been performed it is fairly safe to recommend higher intake of fish and especially omega-3 LCPUFAs, which can be found in fish and seafood. Nevertheless, linoleic acid and transunsaturated fat seem to be quite surely prejudicial to early AMD and could counteract the omega-3 benefic effect and so vegetable oils and processed foods should be avoided.

It should be noticeable that there have been more studies on progression to late AMD and we could say that antioxidant, lutein, zeaxanthin and omega-3 LCPUFA intake should be recommended as secondary prevention treatment in patients with a diagnosis of AMD.

Smoking is still the only solid modifiable risk factor for AMD and should be recommended to all patients at risk or with a diagnosis of AMD to stop smoking.

As many studies have already proven important relationships with specific nutrients, it is to our understanding that more studies regarding types of diets could enlighten better protective food groups or even dishes, which could be recommended to populations at risk – the first evidence of these has also been rendered, but more studies should follow

if Mediterranean and healthier diets including antioxidants, carotenes and omega-3 are in fact more important that these nutrients alone.

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APPENDIX A – AREDS (Age Related Eye Disease Study) AMD Classification System[5]

Stage	Classification	Characteristics
No AMD	AREDS Category I	None or a few small drusen (<63 microns diameter).
Early AMD	AREDS Category II	Any or all of the following: multiple medium drusen (63-124 microns in diameter), or RPE (Retinal pigment epithelium) abnormalities.
Intermediate AMD	AREDS Category III	Any or all of the following: extensive intermediate drusen, and at least one large druse (≥125 microns in diameter), or geographic atrophy not involving the center of the fovea.
Late AMD	AREDS Category IV	Is characterized by one or more of the following in one eye (in the absence of other causes): • Geographic atrophy of the RPE and choriocapillaris involving the center of the fovea • Neovascular maculopathy[1] such as: o Choroidal neovascularization (CNV); - Serous and/or hemorrhagic detachment of the sensory retina or RPE; o Retinal hard exudates (a secondary phenomenon resulting from chronic leakage from any sources); o Sub-retinal and sub-RPE fibro vascular proliferation; o Disciform scar.

[1]Characteristic of "wet" (exudative) AMD.