Nutritional and smoking advice to patients with or at risk of age-related macular degeneration by optometrists in Singapore

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Age-related macular degeneration (AMD) is the leading cause for visual impairment and blindness registration in the developed world. Globally, 8.7% of the population has AMD and it has been projected that the number of people afflicted with AMD by 2020 will be 196 million, increasing to 288 million by 2040.
AMD is multi-factorial and the key pathogenesis of AMD is not known, but it has been postulated to be related to oxidative stress. As there is no known treatment for atrophic AMD, many researchers have investigated the modifiable risk factors such as smoking and diet to prevent progression to neovascular AMD. Following large clinical trials such as AREDS and AREDS 2, many supplements to support eye health emerged in the market. With such a large selection of products and various information, this could be confusing for the patients and even eye care practitioners.

This doctorate programme consists of three distinct studies (chapters three to five) and the first objective of this research was to evaluate the nutritional and smoking advice for patients with or at risk of AMD by optometrists in Singapore. This objective was achieved via a questionnaire (online and hardcopy) (chapter three) as well as face-to-face in-depth interviews (chapter four).

The questionnaire consisted of 41 questions and participants received the hardcopies through mail or an online link through social media or email to complete the questionnaire electronically. The questionnaire elicited demographic information, frequency of dietary advice to patients with early, advanced or at risk of AMD, as well as smoking advice to AMD patients.
The response rate of the questionnaire was 18.2%. 52.9% of the respondents provide dietary advice to patients with advanced AMD most of the time, and 31.7% of the respondents provide dietary advice to patients at risk of AMD most of the time. Optometrists in Singapore advise AMD patients to consume green leafy vegetables and oily fish but seldom advise on the amount to consume. Slightly more than one-third of the optometrists in Singapore will inform smokers of the link between smoking and AMD and slightly more than half will advise AMD patients to stop smoking.
From the face-to-face in-depth interviews, Singapore optometrists do believe that nutrition are beneficial for the eye but they need more knowledge and a guideline in this area to be more confident when providing nutritional advice for AMD patients.

The second objective of this research was to evaluate a Clinical Decision-Making Aid (CDMA) in the form of a flowchart to determine its impact on the self-efficacy of qualified and student optometrists in providing dietary advice regarding risk or progression of AMD (chapter five). The results show that the self-efficacy scores increased after using the CDMA for both qualified and student optometrists and the number of correct answers for five simulated clinical scenarios also increased after using the CDMA.

Despite some conflict regarding nutritional research for AMD, provision of appropriate nutritional and smoking advice is important with regard to reducing risk of progression to sight loss related to AMD. Moreover, optimising nutritional intake and avoiding smoking are beneficial for general well-being. This thesis shows that, with the CDMA, eye care practitioners are able to provide more accurate and research-based nutritional information to their AMD patients with more confidence.

Keywords: age-related macular degeneration, nutrition, smoking, flowchart, survey

For my parents (Kee Peng and Chin Lan), husband (Chee Kean) and daughter (Mikaela)

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List of Abbreviations

ApoE	Apolipoprotein E
AREDS	Age-related eye disease study
ARMS2	Age-related maculopathy susceptibility 2
AMD	Age-related macular degeneration
BDES	Beaver Dam Eye Study
BLD	Basal laminar deposits
BMES	Blue Mountains Eye Study
C2	Complement component 2
C3	Complement component 3
CAREDS	Carotenoids in Age-related Eye Disease Study
CARMIS	Carotenoids in Age-Related Maculopathy in Italians Study
CETP	Cholesteryl ester transfer protein
CDMA	Clinical decision-making aid
CFB	Complement factor B
CFH	Complement factor H
CFI	Complement factor I
CNV	Choroidal neovascularization
DHA	Docosahexaenoic acid
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
EGF	Epidermal growth factor
EPA	Eicosapentaenoic acid
EUREYE	European Eye Study
GA	Geographic atrophy
HDL	High density lipoprotein
HMCN-1	Hemicentin-1
HTRA1	High temperature requirement factor A1
LALES	Los Angeles Latino Eye Study
LDL	Low density lipoprotein
LAST	Lutein Antioxidant Supplement Trial
LIPC	Hepatic lipase
MAC	Membrane attack complex
MDA	Malondialdehyde
MMP	Matrix metalloproteinases
MP	Macular pigment

List of Abbreviations

MPOD	Macular pigment optical density
NHANES	National Health and Nutrition Education Evaluation Survey
NHS	Nurses' Health Study
NICE	National Institute for Health and Care Excellence
OCT	Optical Coherence Tomography
PE	Phophatidylethanolamine
PED	Pigment epithelial detachment
PIGF	Placental growth factor
POLA	Pathologies Oculaires Liées à l'Age
PUFA	Polyunsaturated fatty acid
QoL	Quality of Life
RCT	Randomized Clinical Trial
ROI	Reactive oxygen intermediates
RP	Retinitis pigmentosa
RPE	Retinal pigmented epithelium
SGD	Singapore dollars
SOA	Singapore Optometric Association
TGF-β	Transforming growth factor-beta
TIMP	Tissue inhibitor of matrix metalloproteinase
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation

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Chapter One: Introduction

1.1. Background to the research

Classification of age-related macular degeneration

Age-related macular degeneration (AMD) is an eye condition affecting the macula of the retina that is responsible for central vision. This condition was originally described by Haab in 1885[1], but the modern era of AMD began during the 1960s when Gass[2] described in details the clinical findings associated with AMD in which he believed that the source of pathology for AMD was at the level of the choroid. Though the exact pathogenesis of AMD is still unclear, the retinal layers that are affected in this condition also include the retinal pigmented epithelium (RPE) and Bruch's membrane.

There are several different AMD classification systems in place from previous large population-based studies such as the Beaver Dam Eye Study[3] (BDES) (The Wisconsin Age-Related Maculopathy Grading System) and the Age-Related Eye Disease Study[4] (AREDS) (AREDS Grading System). The AREDS classified AMD with the following system:

Category 1: *No AMD.* No drusen, or a few small drusen ($\leq$ 63 μm in diameter).

Category 2: *Early stage AMD.* Any or all of the following: multiple small drusen or a few intermediate drusen (63-124 μm in diameter) in one or both eyes, or RPE abnormalities.

Category 3: *Intermediate AMD.* Any or all of the following: extensive intermediate drusen and at least one large drusen ($\geq$ 125 μm in diameter) in one or both eyes, or geographic atrophy not involving the center of the fovea.

Category 4: *Advanced AMD.* Geographic atrophy (GA) involving the fovea or abnormal and fragile blood vessels under the retina (neovascular form).

In 2013, Ferris et al.[5] proposed a unified classification scheme which achieved consensus among AMD experts: 1) No apparent aging changes (No drusen and no AMD pigmentary abnormalities), 2) Normal aging changes (Only drupelets (small drusen ($\leq$ 63 μm) and no AMD pigmentary abnormalities, 3) Early AMD (Medium drusen $>$63 μm

and ≤ 125 μm and no AMD pigmentary abnormalities, 4) Intermediate AMD (Large drusen >125 μm and/or any AMD pigmentary abnormalities, 5) Late AMD (Neovascular AMD and/or any geographic atrophy)

Alternatively, AMD can be simply divided into the non-exudative or atrophic type and the exudative or neovascular type, and in addition to simplicity, the two types also offer a natural division in prognosis, as up to 88% of vision loss attributed to AMD is found in the exudative form[6]. Non-exudative AMD often occurs during the early stage of AMD and is characterized by the deposition of basal laminar deposits (BLD) debris at the level of Bruch's membrane and this debris is thought to originate from incomplete metabolism of degenerating RPE cells. The clinical manifestations of AMD is defined by the degeneration of RPE and the accumulation of metabolic byproducts from RPE dysfunction[7]. The earliest stage of dry AMD begins when the BLD have formed a thin continuous layer, and as AMD progresses, the RPE layer continues to degenerate, and two other hallmark findings, drusen and retinal thinning, become manifest clinically[8].

Drusen are localized deposits of membranous deposits that lie between the RPE basement membrane and the remainder of Bruch's membrane. Drusen can be divided clinically into hard or cuticular drusen, soft or granular drusen, and diffuse or confluent drusen. Drusen has long been associated with AMD and the type of drusen can determine if the patient is at risk of exudative AMD[9]. Hard drusen are thought to represent a localized area of RPE dysfunction, are usually smaller than fifty microns in size and have been shown to be unrelated to increasing age[3]. In addition, the presence of small drusen does not increase the risk of progression to late maculopathy[3]. Soft drusen display ill-defined borders, tend to be variable in size and shape, are larger than fifty microns, increases with age and can coalesce to become confluent drusen[10]. The clinical finding of confluent drusen is thought to represent a more diffuse pattern of RPE dysfunction, and Green highlighted that the coalescence of several soft drusen could alter the clinical diagnosis of drusen to serous RPE detachment or exudative AMD[9].

Reticular pseudodrusen, also known as subretinal drusenoid deposits, represent a morphological change to the retina. Histologically, reticular pseudodrusen have been shown to have distinct compositions in comparison to typical drusen and are located above the level of the RPE[11]. It is highly related to later stages of AMD such as choroidal neovascularization and geographic atrophy, but also other diseases such as Sorby's fundus dystrophy, pseudoxanthoma elasticum and acquired vitelliform lesions[11].

Geographic atrophy (GA) of the RPE is the end-stage maculopathy in non-exudative AMD[12], and retinal function in the area of GA is severely compromised. However, the loss of visual acuity is variable as the area of fixation is sometimes spared, even when large areas of atrophy are present. GA accounts for 12% to 21% of legally blind eyes in AMD[13].

Exudative AMD is distinguished from non-exudative AMD when the integrity of the Bruch's membrane or RPE complex separates and forms a pigment epithelial detachment (PED)[7]. When this occurs, the sub-RPE and sub-retinal potential spaces are exposed to the rich vascular milieu of the choriocapillaris and the result is the formation of a pigment epithelial detachment (PED) and exudative AMD. PEDs come in various clinical appearance such as confluent drusen, serous, hemorrhagic and vascular pigment epithelial detachments[14]. Once a PED forms, there are four potential outcomes: persistent PED, spontaneous flattening of the PED, spontaneous RPE tear, or choroidal neovascularization (CNV)[7]. Spontaneous flattening of PEDs has been reported to lead to GA[15,16]. The most common complication of PED is the formation of CNV, which occurs frequently with all of the PED groups except confluent drusen[17]. CNV develops when a defect occurs in the Bruch's membrane and new capillaries from the choriocapillaris grow towards the pigment epithelium[18]. Type I CNV occurs when the neovascularization is confined to the sub-RPE space and Type II occurs when the neovascularization penetrates the RPE to enter the sub-retinal space[19]. CNV can also be classified into classic, occult and disciform scar[7].

Causes and risk factors of AMD

Similar to many other chronic degenerative diseases, AMD is multifactorial. The known factors are environmental, genetic, and sometimes concomitant systemic disease. The term AMD has itself suggested that aging is associated with a higher incidence, and in fact, age is the primary risk factor for AMD. The free radical theory of aging identifies reactive oxygen intermediates (ROIs) as causing cumulative damage to DNA and other macromolecules, leading to senescence, cell death, disease, and ultimate organism death[20]. Oxygen is essential for aerobic activities in living things, but is potentially toxic when harmful molecules known as ROIs are being formed. ROIs can be formed endogenously through normal metabolism and they can destruct many cellular components such as lipids, proteins and nucleic acids[7]. Lipid peroxidation can be initiated by hydroxyl radical (formed as a result of hydrogen peroxide obtaining another electron), hydroperoxyl radical, or singlet oxygen, and toxic compounds that result from lipid peroxidation, such as malondialdehyde (MDA), can cause inflammation either at the site of formation or at other sites via diffusion[7]. ROIs can cause DNA damage or inhibition of transcription and translation through base hydroxylation and cross-linking of DNA strands[21].

Potentially Harmful ROI	**Sources**
Superoxide anion radical, $O_2^{\cdot-}$	Auto-oxidations, oxidases, electron transport chain, respiratory burst, light and lipofuscin
Hydrogen peroxide, H_2O_2	Electron transport chain, light and lipofuscin
Hydroxyl radical, $OH^{\cdot}$	Fenton reaction, Haber-Weiss reaction
Peroxide radical, $ROO^{\cdot}$	Hydroxyl attack of rod and cone polyunsaturated fatty acids after RPE phagocytosis
Singlet oxygen, $^1O_2$	Light acting on molecular oxygen in the presence of photosensitizers such as lipofuscin

Table 1.1: Most common ROI and their possible production sites[7].

Oxidative stress occurs when there is an excess generation of oxidants through essential biologic functions, or an imbalance between oxidants and antioxidants. Besides AMD, oxidative stress contributes significantly to other age-related diseases such as atherosclerosis, chronic lung disease and Alzheimer's disease[22–24]. The eye is highly susceptible to oxidative processes due to its function; it is subjected to high light incidence and in conjunction with photosensitizers such as melanin, rhodopsin and lipofuscin, it has the ability to produce a multitude of ROIs[7]. As oxidative stress has been identified as one of the main causes for AMD, the use of antioxidants such as vitamin C, vitamin E and carotenoids in protecting against development of AMD or limiting its progression have been studied extensively by researchers. Environmental factors such as cigarette smoke contains an extremely high concentration of free radicals[25], causing an increased state of oxidative stress in the body. A meta-analysis of three large population-based studies on three different continents found an odds-ratio for all types of AMD of 3.12 for current smokers compared to non-smokers, and it was concluded that smoking is the main preventable risk factor associated with AMD[26].

AMD is believed to be a genetic condition and over the past few years, many studies were conducted in identifying causative and protective genetic variants associated with AMD, and the discoveries of the complement factor H (CFH) gene and the chromosomal 10q26 locus, which contains the LOC387715/ARMS2 and HTRA1 genes are one of the major breakthroughs[27,28]. Other established genetic risk markers identified include complement component 3 (C3), complement component 2 (C2) or complement factor B (CFB), complement factor I (CFI) and apolipoprotein E (ApoE) [29–32]. Further details will be discussed in the section "Pathogenesis of age-related macular degeneration" in chapter two. In general, the non-modifiable risk factors of AMD are age and genetics, while the modifiable risk factors are lifestyle modifications such as to quit smoking for smokers, or to increase the intake of micronutrients such as antioxidants in their diet.

Singapore Context

Singapore has a population of approximately 5.6 million and 9.72% are aged 65 years and above[33]; the life expectancy at birth for males is 80.7 years and 85.2 years for females[34]. With the rapidly greying population, the prevalence of AMD in Singapore will most likely increase concurrently[35,36]. Singapore is a multi-racial country and the three main races are Chinese, Malays and Indians. The age-standardized prevalence of early and late AMD in Singapore is 5.1% and 0.5% respectively, with no racial predilection, although early AMD is more common in Chinese and Indians compared to Malays[37]. Additionally, the study by Cheung et al. highlighted that the prevalence of bilateral AMD between Singapore Malays and Caucasians is comparable[37].

AMD causes a huge impact on society, and Brown and colleagues found that mild AMD caused a 17% decrease in quality of life of the average patient, moderate AMD caused a 32% decrease in the average patient's quality of life, severe AMD caused a 53% in quality of life and very severe AMD caused a 60% decrease in the average AMD patient's quality of life (QoL), similar to that encountered with end-stage prostate cancer or a catastrophic stroke[38]. Similarly as demonstrated by more recent studies, the vision and health-related QoL scores in AMD patients are reduced significantly[39,40]. It has also been established that early AMD lesions are associated with lower self-reported vision-specific health-related QoL but not general health-related QoL, and the severity and bilaterality of AMD are associated with lower health-related QoL scores[40]. As AMD affects the central vision, the QoL reduces concurrently with the severity of the condition. Therefore those who are visually impaired experience significantly reduced QoL, which manifests as greater social dependence, difficulty with daily living, higher rates of clinical depression, increased risk of falls, premature admission to nursing homes and suicide[41]. Unsurprisingly, the economic burden of AMD in Singapore is high as well and it has been proven by Saxena and co-workers that the medical cost of treating a cohort of patients with category 3 and 4 AMD ranged from Singapore dollars (SGD) 282.8 million to SGD 510.7 million for a period of five years depending on the type of treatment[42]. In view of

the society impact and financial burden that AMD will bring, Singapore initiated the AMD awareness week from 2005. Since then, this public health campaign is organized annually, with the main objective to generate awareness and understanding of AMD, including the modifiable risk factors, through education, early detection and knowledge of treatment and rehabilitation options for the disease. This campaign encourages those above 50 years of age to go for regular eye examinations, and it hopes to preserve vision and improve quality of life of individuals with AMD[43]. The activities of this campaign include educational health talks on AMD, eye screenings for the public above 50 years of age, smoking cessation campaigns and educational and art exhibitions on AMD. This national campaign has produced satisfying results as through a telephone survey conducted in 2006 and 2011, it showed that the awareness of AMD have increased four-fold from 7.3% to 28.1%[44]. Additionally, among the respondents who were surveyed in 2011, 84.1% were aware that smoking is a risk factor of AMD, compared to 45.9% who were aware in 2006.

This public health campaign is indeed necessary as it has been estimated that there will be a growth of 42% in the number of wet AMD cases by 2030, and the estimated economic burden of wet AMD by then is SGD 203.1 million if patients were not taking preventive antioxidant vitamins[45]. On the other hand, if AMD patients were taking preventive antioxidant vitamins, the estimated economic burden would be SGD 162.9 million[45]. In a study by Saxena and colleagues on a hypothetical cohort of category 3 and 4 AMD patients from Singapore, it was found that more than 5400 patients could be prevented from progressing to wet AMD if AREDS formulation were prescribed[42].

From a national perspective, Singapore has recognized AMD to be one of the health conditions that will have a social impact and economic burden to the country in the near future. Hence efforts have been made to increase the awareness of AMD to the public through the national health campaign, AMD awareness week, that is being held annually, and still ongoing till today. Additionally, it hoped that Singaporeans who are aged 50 years and above will go for their annual eye examinations so that AMD could be

diagnosed early, and AMD patients could be more conscious of the modifiable risk factors such as smoking and dietary modification. The role of optometrists is vital as they will most likely be the first health care practitioner to diagnose AMD through a comprehensive eye examination, especially when the patient has no symptoms during the early stages. On top of that, their advice to AMD patients, such as to quit smoking if they are current smokers, to make some changes to their diet, or to take supplements is also important as it could help to prevent their AMD conditions from worsening.

1.2. Scientific justification for the research

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness registration in the developed world[46] and it accounts for 8.7% of all causes of blindness globally[47]. As discussed in the previous section, AMD is classified into non-exudative and exudative forms, and to date treatment is only available for the exudative form. Therefore, researchers are investigating the modifiable risk factors for AMD such as smoking and dietary modification that includes intake of antioxidant micronutrients and/or polyunsaturated fatty acids, and exploring the possibilities of preventing or reducing the risk of progression from non-exudative to exudative AMD, which usually has the worse visual prognosis among all the AMD stages.

Smoking increases the risk of AMD as it increases retinal oxidative stress, decreases choroidal blood flow, stimulates choroidal neovascularization and reduces the amount of antioxidants in the blood[48]. AMD has also been shown to be positively correlated with the duration of smoking and the number of cigarettes[49]. Cross-sectional studies that showed a relationship between smoking and AMD include the Beaver Dam Eye Study[50], Beaver Dam Offspring Study[51], Rotterdam Study[52], Blue Mountains Eye Study[53], Age-related Eye Disease Study[4], Eye Disease Case-Control Study[54] and POLA study[55]. The above-mentioned studies highlight that current smokers have a higher risk of early[51] and neovascular AMD[50,52-53], and the Rotterdam study[52] found that the increased risk of neovascular AMD was present up to twenty years after cessation of smoking.

Longitudinal studies with a follow-up period between five and ten years also proved that current smokers have a higher risk of AMD[56–60].

The first piece of evidence to suggest the association between antioxidant micronutrients in the diet and AMD is from the first National Health and Nutrition Examination Survey that was conducted in the United States back in 1988[61]. With oxidative stress being identified as one of the key pathogenesis of AMD, antioxidant micronutrients in the diet have been of particular interest to many researchers as antioxidants have been known to remove reactive oxygen intermediates (ROIs) in the body[62]. The Age-related Eye Disease Study (AREDS)[63] was the first large clinical trial that evaluated the effectiveness of high-dose antioxidant supplementation in decreasing progression of AMD and associated vision loss. In this trial, the participants in the treatment group received the AREDS formulation consisting of 500mg of vitamin C, 400IU of vitamin E, 80mg of zinc, 2 mg of copper and 28,640IU of vitamin A. The results from the AREDS showed that the AREDS formulation is beneficial for patients with AMD of category 3 or 4[63]; at five years, the estimated probability of progression to advanced AMD was 28% for those assigned to placebo, 23% and 22% for those assigned to antioxidants and zinc, respectively, and 20% for those assigned to antioxidants and zinc. Estimates of risk reduction from odd ratios suggest risk reductions for those taking antioxidants alone or zinc alone of 17% and 21%, respectively, and the risk reduction for those taking antioxidants plus zinc was 25%. In addition, compared with the placebo group, AMD patients in categories 3 and 4 assigned to antioxidants and zinc had a statistically significant reduction in the odds of a 15-letter or greater visual acuity decrease ($p = 0.008$). There is an estimated 27% odds reduction in the visual acuity outcome for this group who are taking antioxidants and zinc. It has been suggested that the reduction in risk of visual acuity loss observed with the antioxidant plus zinc formulation may be a result of the reduction in risk of progression to advanced AMD.

Out of 10 years of follow-up, there were no serious adverse effects and no significant effect on mortality was seen among participants randomized to antioxidant vitamins.

However, there were some concerns on the AREDS formulation for smokers as it was highlighted by other researchers that beta-carotene in the formulation could increase the risk of lung cancer in smokers. Therefore in AREDS 2[64], beta-carotene was replaced by other carotenoids, lutein and zeaxanthin, to establish the efficacy of the new formulation. Besides that, the AREDS 2 evaluated if the addition of omega-3 long-chain polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and lowering the dosage of zinc from the original AREDS formulation would affect the progression of AMD. From the AREDS 2, 10mg of lutein and 2mg of zeaxanthin reduced the risk of progression of AMD, as compared to the group not receiving this combination. Seddon et al. found that 6mg of lutein and zeaxanthin can also be beneficial to AMD patients as it reduces the risk of advanced AMD[65]. Unfortunately, only 1 to 3 mg of lutein and zeaxanthin are obtained from the typical American diet daily[65]. The intake of lutein and zeaxanthin has been found to reduce the risk of late AMD[66], neovascular AMD[67,68], as well as any form of AMD[55,69]. Macular pigment levels have recently been used as an indicator for macular health, hence some studies evaluated the macular pigment optical density (MPOD) following the intake of lutein and zeaxanthin. The studies that revealed increased MPOD following intake of lutein and zeaxanthin include studies conducted by Johnson et al.[70], Zeimer et al.[71], Richer et al.[72] and Huang et al.[73]. Besides increased MPOD, studies such as the Carotenoids in Age-Related Maculopathy in Italians Study[74] (CARMIS) and the Lutein Antioxidant Supplement Trial[75] (LAST) also showed improved visual acuity, contrast sensitivity, Amsler grid results and glare recovery following supplementation of lutein and/or zeaxanthin.

More recently, it was discovered that a deficiency in polyunsaturated fatty acids (PUFAs) would increase the risk of AMD, and this could be because DHA accounts for 50 to 60% of the total fatty acid content of the photoreceptor outer segments[76]. The US Twin Study of Age-related Macular Degeneration[77] and AREDS[78] found that those consuming the highest amount of omega-3 fatty acids had a reduced risk for any stage of AMD and neovascular AMD respectively. Furthermore, they found that the intake of omega-6 fatty

acids had an influence on the results. Prospective studies that showed participants with a high intake of fatty acids have a reduced risk of AMD include the Nurses' Health Study and the Health Professionals' Follow-Up Study[79], Blue Mountains Eye Study[80] and EUREYE[81].

Nevertheless, not all studies on nutrition and AMD showed positive results. There are some evidence suggesting that dietary modification are not beneficial for AMD progression, and a few studies even show that it could cause AMD to progress faster. These studies will be discussed under section 2.3 "Age-related macular degeneration and nutrition" in chapter two. However these studies are only a minority and many researchers still do believe that dietary modification such as increasing intake of antioxidants, lutein, zeaxanthin and polyunsaturated fatty acids are beneficial for AMD patients. Moreover, currently this seems like the most feasible approach as it has proven to be relatively effective and does not cause much damage to the human body, but to be more wary if the AMD patient has other systemic conditions, or is taking other medications.

1.3. Purpose and objective of research

This thesis consists of three different research studies and each has its own purpose and objective. The first study titled "Nutritional and smoking advice to patients with or at risk of AMD by optometrists in Singapore" aims to understand the nutritional and smoking advice that optometrists in Singapore are providing to their patients who have AMD, or are at risk. The second study "What do Singapore optometrists feel about providing nutritional advice to patients with or at risk of AMD?" complements the first through qualitative methods in order to gain a deeper understanding of optometrists' views on nutrition and the eye. The third study "Evaluation of a clinical decision-making aid for qualified and student optometrists when providing nutritional advice for patients with or at risk of age-related macular degeneration" evaluates the efficacy of a clinical decision-

making aid (CDMA) when providing nutritional advice to patients with or at risk of AMD. The following sections will explain in details the purpose and objective for each study.

Study 1: Nutritional and smoking advice to patients with or at risk of AMD by optometrists in Singapore (Chapter 3)

As there is no known treatment for non-exudative AMD, the modifiable risk factors such as smoking and diet modification have been identified to prevent AMD from progressing to exudative AMD or vision from deteriorating. In the early stages of AMD, patients could be asymptomatic and diagnosed of AMD following a routine eye examination. Since there is currently no treatment for non-exudative AMD, patients, particularly those with early stage AMD are usually not referred to the ophthalmologist and instead are asked to self-monitor their central vision at home with an Amsler grid and annual review. Patients who are being referred to the ophthalmologists are usually also being reviewed on a yearly basis, depending on the severity of the condition. Meanwhile, AMD patients could be advised to quit smoking if they are currently smoking, or to increase their intake of certain antioxidants such as vitamin A, C, E and/or lutein and zeaxanthin as well as polyunsaturated fatty acids as these could reduce their risk of exudative AMD. The intake of these micronutrients could be via their diet or nutritional supplements. Therefore, AMD patients may be asked to increase the intake of certain foods in their diet such as green leafy vegetables as they contain high amounts of lutein, or oily fish such as salmon, which is a source of PUFAs. Alternatively, some optometrists may ask AMD patients to get supplements that contain the above-mentioned antioxidants or nutrients which are beneficial for their condition. With the modifiable risk factors being the most feasible management option for patients with non-exudative AMD, the nutritional and smoking advice given by their optometrists is crucial as it could help to prevent a patient's current AMD condition from advancing to later stages and prevent their vision from worsening, especially when there is a family history of AMD or patient is more than 85 years old[82]. In Singapore, there has been no previous research done on this area and not much is

known on the advice optometrists are providing to their AMD patients. In this study, the aim is to understand the smoking and nutritional advice given by optometrists in Singapore to their patients who are at risk or have AMD via a questionnaire, and this aim is achieved via the following objectives:

- To establish the frequency and dietary advice given to patients with early (category 1 or 2) AMD
- To establish the frequency and dietary advice given to patients with established (category 3 or 4) AMD
- To establish the frequency and dietary advice given to patients considered to be at risk of AMD
- To establish the frequency of taking a smoking history in new and review patients
- To establish the frequency of informing smokers of the link between smoking and AMD and advising patients to stop smoking
- To establish the nutritional supplements recommendations to patients with established AMD or at risk of developing AMD
- To establish the confidence level of Singapore optometrists when providing nutritional advice to patients with or at risk of AMD

Study 2: What do Singapore optometrists feel about providing nutritional advice to patients with or at risk of AMD? (Chapter 4)

In order to have a deeper understanding on optometrists' views regarding nutrition and the eye, one-to-one interviews were conducted with fully registered optometrists working in different practices: retail optical shops, clinical optical shops, teaching institutions and eye hospitals or eye clinics; details on the different practices will be elaborated further in chapter four. Singapore optometrists are not legalised to use diagnostic drugs in their practice, hence in this study, one of the objectives is to understand from the participants whether they think diagnostic drugs are beneficial in diagnosing AMD. The other

objectives of this study are as follows:

- To understand optometrists' views on nutrition and the eye, and the eye conditions that they think will benefit from nutrition
- To understand their patients' receptiveness when they provide nutritional advice to them
- To understand how they feel about providing nutritional advice to their patients in their practice, the factors that influence whether or not to provide nutritional advice, and the challenges when doing so
- To establish if they routinely screen for AMD in their practice for patients aged 50 years and above, and whether they think the use of diagnostic drugs will aid in their diagnosis of AMD
- To understand what can be done to support optometrists in their professional development relating to nutrition and the eye

Study 3: Evaluation of a clinical decision-making aid for qualified and student optometrists when providing nutritional advice for patients with or at risk of age-related macular degeneration (Chapter 5)

There are currently various supplements available in the market that are marketed to preserve and/or improve eye health, including AMD. This could be confusing for patients[83,84] and even optometrists, as they are often unsure of the indications to consume them, or which supplements are most beneficial for AMD patients. Hence the aim of this study is to evaluate the efficacy of a clinical decision-making aid (CDMA) that can assist optometrists in providing the most accurate and evidence-based nutritional advice to patients who are at risk, or with AMD. This CDMA is in the form of a flowchart and designed according to the results of AREDS 1[4] and 2[85]. The aim is achieved by investigating if there is a difference in confidence levels via self-efficacy surveys and number of correct answers before and after using the CDMA when providing nutritional

advice for five hypothetical clinical case scenarios. This study is conducted on fully registered optometrists as well as student optometrists to compare the results between the two groups.

This chapter highlighted AMD classification, including the clinical appearance and retinal layers involved at different stages of AMD, the causes and risk factors of AMD, along with the AMD situation in Singapore. In addition, the scientific justification of this research was discussed, together with the objective of each study. In the next chapter, a thorough literature review of the research will be discussed, which includes the epidemiology of AMD in different geographic locations of the world, the more well-known pathogenesis of AMD such as genetic factors and oxidative stress, as well as nutrition and smoking and AMD. To conclude the next chapter, studies that evaluated the nutritional and smoking advice by eye care practitioners to AMD patients will also be reviewed.

Chapter Two: Literature review

In the previous introductory chapter, AMD classification, causes and risk factors were explained. In this chapter, there will be a discussion on the epidemiology and pathogenesis of AMD, including a literature review on nutrition and smoking and AMD. Moving on to the next chapter, details of the first study "Nutritional and smoking advice to patients with or at risk of AMD by optometrists in Singapore" will be discussed.

The Aston Library's Smart Search allows its users to access to a wide range of resources via several databases such as the Cochrane Library, Ovid Journals, ScienceDirect, SpringerLink, Wed of Science and Wiley Online Library, and the relevant journal articles in this literature review was obtained via this system. The Google Scholar was the next platform to gain access to a journal article should it be unavailable in Aston Library. In the event that a journal article was not available from both platforms, it was requested via the Aston Library's Inter-Library service.

The search strategy to identify relevant journal articles used the terms and combination searches outlined in the box below. There were duplications arising from the combination searches and further suitable articles were identified for this review through references within relevant articles.

Terms used in initial searches:

1. Age-related macular degeneration
2. Pathogenesis
3. Nutrition
4. Nutritional advice
5. Smoking
6. Singapore

Combination searches	Hits	Relevant articles
[terms #1] AND [terms #2]	174	50
[terms #1] AND [terms #3]	87	48
[terms #1] AND [terms #5]	224	14
[terms #1] AND [terms #4]	18	6
[terms #1] AND [terms #6]	40	8

2.1 Epidemiology of age-related macular degeneration

As the term suggests, AMD is associated with age and with an increasing ageing population worldwide, the prevalence of AMD will increase exponentially. In 2017, 12.7 per cent of the global population is aged 60 years or over and by 2050, this figure is expected to almost double and rise to 21.3 per cent[86]. Globally, 8.7% of the population has AMD and it has been projected that the number of people afflicted with AMD by 2020 is 196 million, increasing to 288 million by 2040[47].

Colijn and colleagues studied the prevalence of early and late AMD across ten countries in Europe from 1990 to 2013 and found that the prevalence of early AMD was 3.5% in those aged 55 to 59 years and 17.6% in those aged 85 years and above; whilst the prevalence for late AMD was 0.1% and 9.8% respectively[87]. It was projected that by 2040, the number of individuals in Europe with early AMD will range between 14.9 and 21.5 million and between 3.9 and 4.8 million for late AMD[87]. In Australia, the prevalence of early AMD among nonindigenous Australians was 14.8% and 13.8% among indigenous Australians. Late AMD was found in 0.96% of nonindigenous participants and 0.17% of

indigenous participants and the prevalence of late AMD increased to 6.7% in nonindigenous participants 80 years or older [88]. The Irish Longitudinal study on Ageing estimated the prevalence of early AMD in the population aged 50 years or older to be 6.6% and the prevalence of late AMD was 0.6%[89]. In the capital of Iceland, the prevalence of early AMD was 12.4% for those aged between 66 and 74 years and 36% for those aged 85 years or older, and the prevalence of exudative AMD and pure geographic atrophy was 3.3% and 2.5% respectively[82]. Jonasson et al. concluded that persons aged 85 years or above have a ten-fold higher prevalence of late AMD than those aged 70 to 74 years[82]. In a systematic review by Kawasaki et al. from four Asian populations, they found that the pooled prevalence estimates of early and late AMD in Asian populations aged 40 to 79 years were 6.8% and 0.56% respectively. However, they were not able to establish the prevalence estimates of AMD in Asians aged 80 years and above due to the small number of subjects in this age category[90].

Historically, AMD has been known to affect whites more than blacks[91], indicating that there is a genetic predisposition for this condition. Genes and age are the two main factors that are linked to AMD, in which most studies showed a common trend that the prevalence of late AMD increases with age [82,87,88]. Over the years, other factors such as smoking has been established to be linked to AMD and details of these factors will be discussed in the next section. Through further research, AMD has now seem to be multifactorial and this could explain the differences in prevalence in various global locations. In addition, the different age groups of the sample population, as well as the different AMD classification systems used in the studies could also affect the prevalence of AMD discussed previously. However globally, there is an increasing prevalence of AMD due to the ageing population in developed countries.

2.2 Pathogenesis of age-related macular degeneration

The exact pathogenesis of AMD may be unknown but through decades of research it has been found to include drusen genesis, lipofuscin genesis, local inflammatory state

genesis and angiogenesis[92]. Druses are clusters of retinal metabolites between the RPE and the Bruch's membrane, impeding the transport of nutrients and metabolites. Immune-chemical examinations have shown that druses contain plasma proteins, lipoprotein (apolipoprotein E), cholesterol-rich lipids, polysaccharides, glycoprotein and plasma amyloid P, responsible for complement inactivation and membrane attack complex (MAC) formation[93]. Further details on the complement system and MAC will be discussed under the section "Immune system-related genes". Lipofuscin, also known as cell-aging factor, is a product of incomplete metabolism of external segments of photoreceptors by phagolysosomes. Due to loss of the protein-lipid membrane tightness, liposome lipofuscin gets into cytoplasm and then to extracellular areas, forming druses as an end result[92]. Lipofuscin has been suggested to be involved in AMD pathogenesis as its molecule contains hybrid flurophor A2-E, a substance that is active in photoreceptors' apoptosis[92]. Excessive levels of lipofuscin and A2-E (a toxic vitamin A dimer) can also damage photoreceptors and choriocapillaris, leading to geographic atrophy[92]. Besides being toxic to the RPE, A2-E has also been shown to activate the complement cascade[94,95].

The pathogenesis of non-exudative AMD is not completely understood and it is suggested that oxidation and inflammation play important roles in the pathogenesis of the disease. The retinal tissue is one of the tissues with the biggest oxygen needs due to the complexity of its metabolism processes. The human antioxidative system consists of enzymatic and non-enzymatic divisions; the enzymatic system includes catalase, glutathione peroxidase and reductase and superoxide dismutase[96]. Zinc, selenium, copper and manganese ions ensures that this enzymatic system is functioning well[96]. The non-enzymatic part of this system includes vitamins E and C, glutathione as well as carotenoids, and especially lutein and zeaxanthin, which are natural components of the macula[97]. Nowak and colleagues highlighted that oxidative stress could be one of the factors involved in the pathogenesis of AMD and suggested the possible protective effect of antioxidants supplementation[98]. The rods and cones in the retina are replaced every

ten days but their outer segments may be at particular risk of oxidative damage because of high concentration of polyunsaturated fatty acids in the photoreceptor outer segment membrane. Docosahexaenoic acid (DHA) is an omega-3 fatty acid that is a primary structural component of the human retina, comprising 50 to 60 per cent of the polyunsaturated fatty acids in the retina, and is found in the membrane of the outer segment of the photoreceptors[76]. Inflammation has been hypothesized to have a role in the pathogenesis of AMD[99], and Medzhitov first introduced the idea of para-inflammation as a tissue adaptive response to noxious stress or malfunction that has characteristics intermediate between basal and inflammatory states[100]. In the aging retina, oxidized lipoproteins and free radicals are major causes of tissue stress and serve as local triggers for retinal para-inflammation. Drusen have been shown to contain proteins associated with immune-mediated processes and inflammation, and inflammatory cells have been found on the outer surface of Bruch's membrane in AMD eyes[101]. The main genetic changes (polymorphism) associated with AMD were found to be genes that regulate inflammation, most notably Complement Factor H (CFH), a circulating protein that inhibits directly or indirectly the three complement activation pathways[102]. In patients with early and late AMD, many CFH polymorphisms have been described[103]. With abnormal CFH, complement system downregulation is defective and excess inflammation may result. Additionally, histological analysis of drusen revealed the presence of complement factors and the terminal membrane attack complex[104]. Chronic subclinical local inflammation of the retina in AMD patients may trigger and/or sustain the damaging process[99,100].

Angiogenesis is the development of new blood vessels from pre-existing vessels and whilst being a crucial process in normal physiology, it is an important pathogenic process in both benign and malignant disease[105]. Abnormal angiogenesis is a hallmark of diseases such as cancer, chronic inflammation and also the neovascular form of AMD[106,107]. Choroidal neovascularization (CNV) represents the growth of new blood vessels from the choroid into the subretinal pigment epithelium. Several proangiogenic

factors are consistently upregulated during CNV formation, particularly two members of the vascular endothelial growth factor (VEGF) family, VEGF-A and placental growth factor (PIGF)[106]. These factors activate quiescent endothelial cells and promote cell proliferation, migration and vascular permeability[106].

Genetic factors

Studies have shown that there is a strong correlation between a family history of AMD and the subsequent development of both early and late forms of the disease. This is proven by higher concordance rates among monozygotic twins when compared with dizygotic, and segregation analyses comparing first degree relatives of affected individuals as compared with the general population[108,109]. The study by Smith and Mitchell showed that the risk of developing late AMD was increased nearly four-fold for those with a family history of AMD, particularly in cases of neovascular AMD[109]. This risk is amplified when immediate family members have the disease, with one study estimating a 27.8 times increase in risk with an affected parent and 12 times increase in risk for those with an affected sibling[110]. As AMD is a multifactorial disease, it is challenging to identify specific genes that are responsible for causing the symptoms of AMD. Despite this challenge, researchers have identified approximately forty genes that may be associated with the development of AMD, and some of these genes fall into broad groups based on their function: genes with retinal-specific function, immune function, neovascularization, or lipoprotein-related function[111].

Genes with retinal-specific function

Unlike retinitis pigmentosa (RP) and other early onset retinal degenerations, retinal specific genes have minimal impact on AMD susceptibility and only three monogenic macular dystrophy-related genes, ABCA4, apolipoprotein E (ApoE) and Tissue inhibitor of matrix metalloproteinase-3 (TIMP-3) show any association with AMD risk[111]. Of these genes, only ABCA4 expression is restricted to the retina while ApoE and TIMP-3 have

additional systemic functions. ABCA4 is a specific marker for photoreceptor cells and found in the outer segment disks of this retinal layer. Its function involves the transportation of N-retinylidene phophatidylethanolamine (PE) across membranes in photoreceptor cells[112]. In the absence of functional ABCA4, a N-retinylidene PE complex accumulates, leading to a buildup of lipofuscin fluorophore A2E[113]. Retinal degeneration in those with compromised ABCA4 may result from loss of the ability to transport N-retinylidene PE out of photoreceptor cells, or RPE toxicity associated with A2E buildup[112]. ABCA4 mutations cause a range of retinopathies such as Stargardt disease and autosomal recessive RP that vary in severity related to the degree of residual retinal function. Despite this, they are not a common cause of AMD[114] and more research is needed to clarify its actual roles in AMD development.

Immune system-related genes

Immunological responses have long been implicated in AMD progression but the pathways involved have remained unclear. The complement cascade can be activated by a number of triggers, usually related to infection, and aids in the destruction of foreign pathogens. The complement system is a crucial component of the body's innate immune system against antigens and it consists of the classical, lectin and alternative cascades [115–118]. These three cascades eventually result in the formation of membrane attack complexes (MAC) that cause cell lysis and inflammation through chemokine release and increased capillary permeability[116,117]. Homeostasis of the complement system is achieved via various proteins and disruption of this balance leads to sustained activation of the complement system, resulting in chronic inflammation and forming druses[119]. Besides the formation of drusen which is a clinical hallmark of early AMD, studies have also shown that the complement system predisposes to choroidal neovascularization (CNV) by increased vascular-endothelial growth factor (VEGF) expression[120,121]. Different components of the complement pathways have been associated with AMD, namely factor H (CFH), factor H-related complement, factor B, factor D, and factors 2, 3

and 5[111]. CFH is a key regulator and major inhibitor of the alternative complement pathway and is found within drusen [115,122], and Y402H is one of the high-risk CFH variants strongly associated with AMD, especially in Western Europeans[123,124]. CFH can be found in the RPE of the retina and the Y402H variant has been found to be associated with the presence of complement proteins in drusen[122,125]. Early genetic studies identified a susceptibility locus on chromosome 10q26 for the development of AMD[126]. Further genomic studies of this chromosome demonstrated two AMD susceptible loci: one is known as rs10490924, which lies within the gene LOC387715/ARMS2, now known as Age-Related Maculopathy Susceptibility 2 (ARMS2), and the other, rs11200628, lies within the promoter region of the gene known as High Temperature Requirement Factor A1 (HTRA1) gene. The precise function of ARMS2 in AMD is largely unknown, but findings have suggested that mitochondrial dysfunction results in AMD, and smokers are at a higher risk of AMD via this gene[127,128]. Therefore this suggests that mitochondrial function is disrupted by ARMS2, leading to the formation of reactive oxygen intermediates (ROIs), apoptosis and AMD[62]. HTRA1 has been shown to be associated with an increased risk of wet AMD in certain populations[126,129]; HTRA1 binds to and inhibits transforming growth factor-beta (TGF-β), a factor known to play a crucial role in extracellular matrix deposition and angiogenesis. Therefore, it is possible that HTRA1 may play a role in the regulation of Bruch's membrane and growth of vessels into the RPE[126]. The two other immune-related genes that are related to AMD are the epidermal growth factor (EGF) containing fibulin-like extracellular matrix protein (ECM) 1 (EFEMP1), also known as fibulin 3, and Hemicentin-1 (HMCN-1). The actual attributable risk of EFEMP1 on AMD development is not known, but its role in extracellular matrix protein alteration and retinal deposits make it a likely player in AMD pathogenesis and further studies are required to define this risk more precisely.

Genes related to neovascularization

VEGF, TIMP-3 and fibulin 5 are genes producing proteins that directly or indirectly influence the growth of new blood vessels[111]. Of these, VEGF is the most important and it is the target of current anti-AMD therapy ranibizumab (Lucentis) and bevacizumab (Avastin). AMD development can be influenced by genes that directly or indirectly influence the levels of VEGF. Vascular endothelial cell growth factor (VEGF) is a member of the platelet-derived growth factors and it plays an important role in maintaining a healthy retina. There are five different retinal cell types that produce VEGF and they include vascular endothelium, retinal pigmented epithelium, Muller cells, ganglion cells and astrocytes[130,131]. There are seven biologically active isoforms in the VEGF family, but VEGF-A is thought to be most critical in the angiogenesis process[111]. VEGF-A has been linked to many ocular neovascular diseases[132] and previous studies have demonstrated that patients with wet AMD, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion and neovascular glaucoma[133] have an increased intraocular levels of VEGF. All of these ocular diseases share a similar pathological process: vascular permeability and neovascularization. VEGF is released by the retina and RPE in response to tissue hypoxia[111]. Increased VEGF production results in subsequent upregulation of endothelial nitric oxide synthase, metalloproteinases and decreased tissue inhibitors of metalloproteinase expression, which together enhance choroidal neovascularization[111]. Single nucleotide polymorphisms at the genetic level are presumed to contribute to altered VEGF and VEGF-2 expression, leading to the pathogenesis of AMD and even diabetic retinopathy. Tissue Inhibitor of Matrix Metalloproteinase (TIMP) refers to a group of proteins that inhibit matrix metalloproteinases (MMPs), a group of proteins involved in extracellular matrix (ECM) degradation. Macular Bruch's membrane concentrations of Tissue Inhibitor of Matrix Metalloproteinase-3 (TIMP-3) appear to be age-dependent[134]. Additionally, patients with AMD often have supra-normal levels of TIMP-3 both in macular Bruch's membrane and in macular drusen. As TIMP-3 inhibits MMPs, excess TIMP-3 may retard Bruch's

membrane renewal and result in the thickening of Bruch's membrane. By reducing Bruch's membrane permeability, the trafficking of metabolites and nutrients between the choroid and RPE is also reduced, ultimately resulting in RPE and photoreceptor atrophy[134]. TIMP-3 acts as a local inhibitor of VEGF thus limiting CNV[135]. Mutations leading to decreased activity in TIMP-3 result in increased VEGF levels and a subsequent increase in the growth of pathological blood vessels in the eye. Many hypotheses have been proposed regarding the direct mechanism and causative relationship between TIMP-3 and AMD development, the direct mechanistic relationship remains unknown and more research is needed to address the mechanistic relationship between these associative findings. The fibulin 5 gene is a member of the same family as EFEMP1/Fbln3. As properly functioning fibulin 5 strengthens cell adhesions, down-regulates VEGF and controls choroidal endothelial cell proliferation, mutations leading to misfolding and subsequent dysfunction of this protein confer an increased risk of AMD development[136].

Lipoprotein-related genes

Hepatic Lipase (LIPC) is responsible for lipoprotein production and the presence of an HDL-elevating allele of the LIPC gene was found to be associated with decreased risk of AMD[137–139]. While high HDL levels are protective against AMD, individuals with high LDL counts have a significantly higher risk of developing AMD[138]. The discovery of LIPC, a genetic variant in the HDL pathway, may serve as a potential marker to be used in laboratory testing and individual risk analysis for the development of AMD[138]. Apolipoprotein E (ApoE) is a plasma protein and regulates the transport of lipid and cholesterol in the central nervous system by serving as a ligand for low density lipoprotein (LDL) receptors[140]. ApoE is found in the liver, brain and in various parts of the eye such as the RPE, Bruch's membrane, photoreceptor cells, retinal ganglion cell layer, choroid, as well as in drusen in early AMD[141]. ApoE consists of three major variants: E2, E3 and E4; the E4 isoform is associated with neurodegenerative diseases such as

Alzheimer's disease[142]. The ApoE4 isoform is also associated with a reduced risk of AMD development, and it has been postulated that this is achieved by suppressing the expression of the chemokine CCL2 (C-C motif ligand 2) and VEGF expression[143]. On the other hand, more studies are necessary to establish the relationship between cholesteryl ester transfer protein (CETP), CD36 and AMD. CD36 is expressed in the RPE and may participate in phagocytosis of photoreceptor outer segments[144,145]. Basal laminar deposits that are found in the early stage of AMD have been shown to contain oxidized LDL, to which CD36 binds[111]. Increases in oxidized plasma LDL are observed with age and high cholesterol diet, and CD36 serves as the primary receptor in RPE cells for oxidized plasma LDL[111].

As a positive family history of AMD increases a patient's risk of getting AMD, it may seem more imperative to provide nutritional and smoking advice to such patients. Whilst genetic factors can provide an indication to practitioners on providing nutritional and smoking advice, previous reports have suggested that genetic testing for AMD may have a role because of potential harmful genetic interaction with specifically the zinc component in the AREDS supplements[146,147]. However, the American Academy of Ophthalmology recommended that genetic testing for AMD should not be conducted prior to considering treatments for AMD such as the AREDS supplements[148].

Oxidative Stress

The aging process occurs as a main result of the free radical reactions that are going on continuously in the cells of the human body[20]. "Oxidative stress refers to cellular damage caused by reactive oxygen intermediates (ROIs) and the retina is highly susceptible to oxidative stress due to its high consumption of oxygen, its high proportion of polyunsaturated fatty acids and its exposure to visible light" [62]. The retina, especially the macula is exposed to a high amount of oxidative stress as it is the highest oxygen-consuming tissue in the body[149] and the high amount of polyunsaturated fatty acids in the photoreceptor outer segments and lipofuscin makes the retina prone to the

generation of ROIs[150,151]. ROIs cause lipid peroxidation of the RPE cell membrane, which may trigger the complement system and lead to chronic inflammation[151], as discussed earlier. It has also been postulated that CFH synthesis and/or secretion is impaired by oxidative stress[152]. Superoxide dismutase, catalase and glutathione peroxidase are antioxidant enzymes and they remove ROIs enzymatically. Vitamins and other carotenoids can also 'scavenge' ROIs either directly or non-enzymatically[62].

Smoking

As mentioned earlier, smoking is one of the modifiable risk factors for AMD and it has been shown to be positively correlated with the duration of smoking and the number of cigarettes[49]. AMD could result from oxidative stress in the retina and smoking exacerbate the condition through further oxidative insults to the retina, decreased choroidal blood flow, increased ischaemia, hypoxia and micro-infarctions, stimulation of CNV and reduction of serum antioxidants[48]. The toxic effect of hydroquinone on retinal cells includes the accumulation of VEGF and the reduction of macular pigment[153,154]. Authors have also found that cigarette smoking causes inflammation by activating complement C3 and other inflammatory mediators and reducing serum levels of CFH[155].

Other systemic risk factors

A higher body mass index (BMI) is another modifiable risk factor that is implicated in the pathogenesis of AMD. Studies such as the Los Angeles Latino Eye Study (LALES) and the Blue Mountains Eye Study (BMES) showed that persons with a high BMI were at greater risk of early AMD, but no significant associations were seen with late AMD[156,157]. The Age-related Eye Disease Study (AREDS) found significant associations between a higher BMI and both subtypes of late AMD[4,158]. It has been postulated that obesity increases the risk of AMD through changes in the lipoprotein profile or an increase in oxidative damage and inflammation as obese persons generally have a diet low in antioxidants and polyunsaturated fatty acids or even an overall unhealthy lifestyle[159].

Besides obesity, hypertension has also been hypothesized as a risk factor for AMD due to its effect on the choroidal blood flow[160,161]. In the Bam Deaver Eye Study (BDES), hypertension was associated with a ten-year incidence of late AMD, in particular CNV [162], and in the Rotterdam Study, a clear dose-dependent association was found between elevated systolic blood pressure and increased risk of incident AMD[163]. On the other hand, the BMES indicated that neither pressure, systolic or diastolic blood pressure, or presence of hypertension at baseline were associated with incident AMD[58].

2.3 Age-related macular degeneration and nutrition

The first National Health and Nutrition Examination Survey conducted in the US provided the first piece of evidence that the intake of fruits and vegetables high in vitamins A and C is associated with the risk of AMD[61]. Since then, researchers work intensively in this area as currently there is no treatment for atrophic AMD and GA, and if AMD progresses to the exudative form, it will have the worst visual prognosis among the other forms. Additionally, oxidative stress has been postulated as one of the more viable pathogenesis for AMD, therefore introducing antioxidants in the form of vitamins or carotenoids would seem promising for AMD patients to prevent their condition from getting worse.

Age-related Eye Disease Study (AREDS)

The first controlled oral intervention study for AMD patients was performed by Newsome et al. where oral zinc was administered in subjects with drusen or macular degeneration [164]. The study showed positive results but oral zinc was not widely used at that time due to the possible toxic effects and complications of oral zinc. The main side effect associated with high doses of zinc is mineral absorption disturbances, and the most serious interactions are with cooper and iron[165]. Therefore there have been reports of cooper deficiency following oral use of high doses (more than 220 mg) of zinc for a period of time (more than ten months)[166]. Other symptoms reported to be associated with high

zinc intake include nausea, vomiting, headache, abdominal cramps, epigastric pain, loss of appetite, lethargy and fatigue. About ten years later, a large clinical trial, the Age-Related Eye Disease Study (AREDS) was conducted with the key aim of determining the effect of high-dose antioxidant supplementation in decreasing the progression of AMD and associated vision loss. AREDS was a multicentred, double-blind placebo-controlled trial involving 3640 subjects aged between 55 and 80 years of age[167]. The AREDS formulation consists of 500mg of vitamin C, 400IU of vitamin E, 80mg of zinc, 2 mg of copper and 28,640IU of vitamin A. A statistically significant reduction in the odds of developing advanced AMD was found in patients receiving antioxidant vitamin supplementation plus zinc, compared with placebo (OR: 0.72; 99% CI: 0.52-0.98). A statistically significant odds reduction was not seen in participants receiving antioxidants and vitamins alone or zinc alone. After removing participants from Category 2 AMD (extensive small drusen, pigment abnormalities, or at least one intermediate size druse), odd reduction estimates reached statistical significance in patients receiving antioxidants and vitamins plus zinc (R:0.66; 99% CI: 0.47-0.91) and in those receiving zinc alone (OR: 0.71; 99% CI 0.52-0.99). Statistically significant odds reduction in vision loss (of 15 or more letters) occurred in patients receiving antioxidants and zinc, (OR: 0.73; 99% CI: 0.54-0.99) and the risk of serious adverse events did not reach statistical significance in any treatment groups of the study. 2% of the study participants discontinued the supplementation as reports from other investigators highlighted the increased risk of lung cancer in smokers taking beta-carotene[168,169].

AREDS 2

In AREDS 2, one of the goals was to determine the effect of the addition of lutein and zeaxanthin, as these carotenoids were not commercially available when AREDS was conducted, as well as the addition of omega-3 long-chain polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Another goal was to assess the effect of the removal of beta-carotene, and lowering the dosage of zinc from

the original AREDS formulation. No statistically significant reduction in risk of progression to advanced AMD was observed beyond the effects of AREDS formulation; however, in secondary exploratory analyses, when patients receiving lutein and zeaxanthin were compared with those not receiving this combination, an added 10% reduction in risk was noted, which was statistically significant (HR: 0.90; 95% CI: 0.82-0.99). In addition, when lutein plus zeaxanthin was substituted for beta-carotene, a significant reduction in risk of progression was observed compared with the original AREDS formulation (HR: 0.82; 95% CI: 0.69-0.96). Last but not least, beta-carotene supplementation was found to be associated with an increased risk of lung cancer in former smokers (2.0% versus 0.9%, P=0.04)[64].

Despite the promising results of AREDS and AREDS 2, a recent review by Macdonald[170] on five randomized clinical trials (RCTs) highlight that antioxidant vitamin or mineral supplements do not prevent age-related macular degeneration. In fact, a multivitamin combination increased the risk of AMD. However, unlike the AREDS or AREDS 2 where a combination of antioxidant vitamins and minerals were evaluated, the RCTs in Macdonald's review evaluated the vitamins (vitamin A or C or E) and minerals (zinc) on its own. Moreover, there was no mention of the ingredients that were in the multivitamin combination, which makes it prejudiced to conclude that multivitamin combination increased the risk of AMD.

Lutein and Zeaxanthin

More than 600 carotenoids are found in nature and lutein is found in greatest percentage in human serum (20%)[171]. Lutein and zeaxanthin are found in the human retina and they form the retinal macular pigment (MP)[172]. Besides improving visual performance, MP also protects the retina against the damaging effects of light and MP levels are used as an indicator of macular health, particularly to predict the likelihood of developing AMD [172]. As discussed in AREDS 2, the beneficial effects of lutein and zeaxanthin may be their ability to protect the retina by absorbing the short-wavelength blue light and

ultraviolet radiation and reducing oxidative stress[64]. There is a huge variety of food that contain lutein and zeaxanthin and the foods that are high in lutein and zeaxanthin include but not limited to, green leafy vegetables such as kale and spinach, egg yolk, broccoli, pumpkin and corn[173]. From the AREDS 2 study, the benefits of lutein and zeaxanthin were from consuming 10 mg of lutein and 2 mg of zeaxanthin daily[64] but consuming 6mg per day of lutein and zeaxanthin has also been found to reduce the risk of advanced AMD[65].

Besides AREDS 2, there were other studies that have been conducted to evaluate the association between intake of lutein and zeaxanthin and risk of AMD, and the results vary among studies. In a secondary analysis of the AREDS 2, lutein and zeaxanthin on top of the original AREDS formulation lowered the progression to advanced AMD, but only in persons with low dietary lutein and zeaxanthin[85]. A systematic review and meta-analysis of six longitudinal cohort studies with a total of 123,178 participants in the British Journal of Nutrition examined the effects of lutein and zeaxanthin on AMD and found a significant risk reduction only in late AMD with an increased dietary intake of these carotenoids (RR: 0.74; 95% CI: 0.57, 0.97)[66]. Another systematic review and meta-analysis by Chong et al. on nine prospective studies involving 149,203 participants showed a statistically significant inverse association between the intakes of lutein and zeaxanthin and neovascular AMD risk. (RR:0.68; 95% CI: 0.51, 0.92)[67]. Case-control studies by the Eye Disease Case-Control Study Group[174] and Snellen at al.[68] involving 132 subjects found that high intakes of lutein were protective against neovascular AMD. Cross-sectional studies found that high plasma levels of zeaxanthin have a reduced risk of any stage of AMD[55,69]; and the combination of lutein and zeaxanthin from the POLA study that recruited 2584 subjects showed the same trend[55]. A cross-sectional analysis of the third cohort of the National Health and Nutrition Education Evaluation Survey (NHANES III) showed that those aged between 40 and 59 and consuming highest levels of dietary lutein and zeaxanthin had less risk for pigment abnormalities compared to those consuming the lowest amounts (OR=0.10; 95% CI: 0.10, 0.30). Additionally,

among those aged between 60 and 79, those consuming the highest level of lutein and zeaxanthin have a reduced risk for late AMD (OR=0.10; 95% CI: 0.00, 0.90). A small interventional study on 150 participants by Bucheli and colleagues showed that elderly supplemented with 13.7g per day of lacto-wolfberry, a potent source of zeaxanthin, for ninety days has increased serum zeaxanthin levels and antioxidant capacity in serum, and their retina showed reduced pigment changes and soft drusen accumulation relative to the placebo group[175]. As mentioned earlier, MP levels are used as an indicator for macular health, hence some studies evaluated the macular pigment optical density (MPOD) following intake of lutein and/or zeaxanthin. Placebo controlled trials revealed that 12mg of lutein a day or a combination of 12mg lutein and 1mg zeaxanthin a day for a period of four months and six months respectively significantly increased macular pigment optical density (MPOD)[70,71]. In a one-year randomized double-blinded placebo-controlled study by Richer and colleagues, 60 patients were divided into three groups: 1) 8mg zeaxanthin a day; 2) 9mg lutein a day; 3) combination of both carotenoids. After a year, MPOD increased in all three groups, and was not different among the groups[72]. In another randomized, double-blinded and placebo-controlled trial on 112 patients with early AMD, it was found that after two years of supplementation with lutein, serum lutein concentration, MPOD and visual sensitivities was increased [73]. In addition, it was concluded that 10mg of lutein daily might be an advisable long-term dosage for early AMD. In a more recent clinical trial on 64 subjects, lutein complex, consisting of marigold (lutein) and wolfberry (zeaxanthin) was found to reduce oxidative stress index and inflammatory markers, and best-corrected visual acuity was lowered in subjects when treated for five months[176]. This suggests that consumption of lutein complex suppresses the oxidative stress and therefore reduce the incident of AMD. Studies such as the Carotenoids in Age-Related Maculopathy in Italians Study (CARMIS) and the Lutein Antioxidant Supplement Trial (LAST), involving 145 and 90 participants respectively, combined lutein and zexanthin with antioxidants and they showed positive results such

as elevated MPOD, improved visual acuity, contrast sensitivity, Amsler grid results and glare recovery[74,75].

However, despite the positive results discussed, there were few studies that did not find any effect of lutein and zeaxanthin on risk for AMD. They include cross-sectional study by Michikawa et. al and cross sectional analyses of the BDES and European Eye Study [177–179]. In the study conducted by Michikawa et. al[179], there was no significant difference in the serum lutein and zeaxanthin levels between normal patients and patients with early or late AMD; and this could be because of the low sample size: 32 early AMD patients and 8 late AMD patients. A few prospective studies also reported the same findings that lutein and zeaxanthin have no effect on AMD risk and they include studies by van Leeuwen et al. (4179 participants), Flood et al. (2335 participants), and VandenLangenberg et al. (1709 participants)[180–182]. In these studies, food frequency questionnaires (FFQs) were used to assess nutrient intakes and this could be a possible source of confounding bias as AMD patients tend to be older and they might not recall correctly and accurately their daily diet intake. Moreover, the follow-up period for the studies conducted by Flood et al.[180] and VandenLangenberg et al.[182] was five years, which could be slightly short for conditions like AMD. Another prospective study that showed lutein or zeaxanthin intake was associated with an increased risk of AMD is a study done on 254 patients by Robman and co-workers [183]. Similar to other prospective studies, this study utilised FFQs to assess patients' nutrient intakes and they used a different AMD classification system other than the ones used in the BDES, AREDS and Rotterdam Eye Study. Robman and colleagues concluded that the AMD patients in their study were aware of their condition before and during the study and hence improve their lifestyle by increasing their intake of carotenoids and PUFAs. As a result, the high levels of carotenoids switched from antioxidant to pro-oxidant, thereby increasing their risk of AMD. On top of that, from the retrospective analysis of the NHANES III cohort that consisted of 8222 participants, it was observed that those who consumed the highest amounts of lutein and zeaxanthin had a slightly increased risk for the appearance of

drusen[184]. In spite of this, the authors concluded that the relation of lutein and zeaxanthin to AMD may be influenced by age and race, therefore require further evaluation in separate populations and in prospective studies.

Lutein and zeaxanthin form the retinal macular pigment and consuming foods high in these carotenoids will serve to protect the macula, and AMD. Most studies, particularly the clinical trials, have shown that lutein and zeaxanthin reduced the risk of AMD, increased MPOD and improved visual acuity.

Polyunsaturated fatty acids

The photoreceptor outer segments are constantly replenishing and DHA accounts for 50 to 60% of the total fatty acid content of the photoreceptor outer segments[76]. Therefore, supplementation of omega-3 long chain polyunsaturated fatty acids (PUFAs) would seem helpful in AMD patients. Additionally, a review by Evans and Lawrenson highlighted that a deficiency in PUFAs would increase the risk of AMD[76]. Omega-3 long-chain PUFAs also play a role against oxidative stress, inflammation and vascular dysfunction, which have been shown to be closely associated to the pathogenesis of AMD[185].

The Nutritional AMD Treatment 2 study that was conducted on 263 subjects found that administering 350mg of EPA and 650mg DHA daily for three years lower the risk of CNV in patients with early lesions of AMD[186]. Red blood cell membranes are long-term biomarkers of omega-3 long-chain PUFAs and they have been found to be strongly associated with neovascular AMD after dietary oily fish and seafood intake[187]. The US Twin Study of Age-Related Macular Degeneration, involving 681 twins, is a cross-sectional study that compared those consuming the least amount of omega-3 fatty acids to those consuming the highest amount of omega-3 fatty acids. In this study, they found that those consuming the highest amount had a reduced risk for any stage of AMD (OR=0.55; 95% CI: 0.32, 0.95) and this effect was driven mostly by those with a low linoleic acid and omega-6 fatty acid intake ($p<0.001$), as the effect vanished in those with

an intake of linoleic acid above the median[77]. The AREDS found that compared to those in the lowest quintile of intake, those in the highest quintile of intake for EPA, DHA and total long-chain omega-3 fatty acids were at a reduced risk for neovascular AMD. However, when the cohort was separated by intake of arachidonic acid, a type of omega-6 fatty acid, the reduction of risk for neovascular AMD became insignificant[78]. A prospective analysis of AREDS revealed that increasing intake of DHA and EPA was associated with a decreased rate of progression to central GA over 12 years (p=0.026). Increasing intakes of DHA alone (p=0.001) or DHA and EPA (p=0.032) were also associated with a decrease in risk of progression to neovascular AMD (p=0.001)[188]. However, from the AREDS 2 study, a daily dose of EPA and DHA together with the AREDS formulation did not offer an additional advantage in reducing the risk of developing advanced AMD[64]. An increased intake of DHA and EPA daily is associated with a reduced risk for progression to advanced AMD and participants who were healthy at baseline benefited from a diet high in DHA as there was a markedly reduced progression of early AMD in these patients[189]. Prospective studies such as the Nurses' Health Study (NHS) and the Health Professionals' Follow-Up Study, BMES and EUREYE also showed participants with a high intake of fatty acids have a reduced risk of AMD [79–81]. Chiu et al. showed that in the AREDS participants, there was no association between DHA intake and risk for drusen (R=0.94; 95% CI: 0.77, 1.16) or late AMD (OR=0.82; 95% CI: 0.59, 1.13); there was also no association between intake of EPA and risk for drusen (OR=0.96; 95% CI: 0.84, 1.15)[190]. There was also no association between intake of EPA, DHA or alpha-linolenic acid and risk for early or late AMD in the Melbourne Collaborative Cohort of 6734 participants[191]. Conversely, some prospective studies showed deleterious effects of omega-3 fatty acid intake on risk for AMD, and they include the Carotenoids in Age-Related Eye Disease Study (CAREDS)[192], consisting of 1787 women, as well as a study by Robman et al[183]. In the CAREDS[192], the fat intake was estimated using FFQs and the AMD patients were followed through

for only four years. The study design by Robman et al. was discussed in the previous lutein and zeaxanthin section.

In 2017, Evans and Lawrenson conducted a review on antioxidant and mineral supplements for slowing the progression of AMD[193]. This review consisted of three large trials with reasonably long treatment duration and follow-up of four to six years (AREDS 2001[194]; AREDS 2 2013[64]; VECAT 2002[195]), and sixteen smaller trials (ranging from 20 to 400 participants) and shorter duration of treatment and follow-up (6 to 24 months). The results of AREDS and AREDS 2 have been discussed previously. The VECAT 2002 study suggested that the general population should not take vitamin E with a view to preventing the incidence or progression of AMD. However, the study was underpowered to answer the question about whether people with signs of AMD should take vitamin E.

The other trials of multivitamin preparations such as Ocuguard[196], Ocupower[75], Visaline[197] and lutein or antioxidant[198] were too small to provide evidence in either way. Pooling results, where possible, did not provide evidence of any benefit of supplementation. However, these trials were of relatively short duration. Newsome 1988[164] found a reduction in the risk of visual acuity loss with zinc supplementation over 12 to 24 months. However, Stur 1996[199] found no effect of zinc treatment. Newsome 2008[200] found that zinc-monocysteine had beneficial effects on visual acuity and contrast sensitivity.

The main evidence that antioxidant vitamin and mineral supplementation was of benefit came from the AREDS trial, and potential biases have been minimised as it was a large, well-conducted randomised study. Other than the AREDS, pooling data from other trials revealed little evidence for effectiveness of antioxidant vitamin and mineral supplements on preventing visual loss or progression of the disease. However, the other studies encompassed many different formulations and in general, were rather small and of short duration, which may explain the lack of effect.

In conclusion, from the AREDS and AREDS 2 results, AMD patients may experience modest delay in progression of the disease with antioxidant vitamin and mineral

supplementation. However, as these two large trials were conducted in a relatively well-nourished American population, we will not know whether these findings can be applied more generally until it is replicated by other large-scale trials in other populations. In addition, this review shows little effect, if any, of supplements containing lutein and zeaxanthin on the progression of AMD but the evidence was low-certainty. Generally, AMD patients should take antioxidant vitamins and zinc at the levels described in this review, and smokers and people with vascular disease should be wary of the harmful effects associated with long-term vitamin supplementation as smokers who take beta-carotene may be at an increased risk of developing lung cancer and among people with vascular disease and diabetes, vitamin E supplementation was associated with a higher risk of heart disease.

2.4 Age-related macular degeneration and smoking

According to World Health Organisation (WHO), the projected prevalence of smokers in Asian countries such as China, South Korea and Singapore in 2025 will be 43.3%, versus Western countries, with a projected prevalence of 16.3%[201]. With the increasing number of smokers, the prevalence of AMD will increase as well as smoking has been shown to be associated with AMD in the following studies. Cross-sectional studies such as the Beaver Dam Eye Study[50], Beaver Dam Offspring Study[51], Rotterdam Study[52], Blue Mountains Eye Study[53], AREDS[4], Eye Disease Case-Control Study[54] and POLA study [202] showed a relation between smoking and AMD. The Beaver Dam Eye Study[50], Rotterdam Study[52] and Blue Mountains Eye Study[53] proved that current smokers had a higher risk of neovascular AMD. Additionally, the Rotterdam Study[52] found that the increased risk of neovascular AMD was present up to twenty years after cessation of smoking. In the Beaver Dam Offspring Study[51], current smoking and greater number of pack years were associated with early AMD. In the POLA study, current and former smokers had an increased prevalence of late AMD and the risk is higher if patients smoked twenty pack-years and more[202].

After five years, the Beaver Dam Eye Study concluded that men who smoked greater number of cigarettes were more likely to develop early AMD, and a ten-year follow-up confirmed that their AMD were also more likely to progress[56,203]. The longitudinal analysis of the Blue Mountains Eye Study after five years concluded that current smokers had an increased risk of incident GA and any late lesions[204]. After ten years, results show that current smokers had a four-fold increase in the risk of late AMD compared with never-smokers, and former smokers had a three-fold higher risk of GA[205]. Current or former vs never smoking participants was associated with a 30% (95% CI, 10-70%) increased risk for progression to either subtype of late AMD in one or both eyes after a mean follow-up of 6.3 years[59]. In a more recent longitudinal study performed on 64,560 South Koreans, it was shown that cigarette smoking is associated with a strong risk of neovascular AMD and the duration of smoking and daily cigarette consumption was associated with the incidence of neovascular AMD in a dose-dependent manner[60]. It has also been established that current cigarette smoking in exudative AMD patients is associated with poor visual acuity improvement following intravitreal anti-VEGF therapy[206].

2.5 Age-related macular degeneration and nutrition and smoking advice

Currently there is still no treatment available for early and atrophic AMD, and despite conflicting results from nutritional research, to advise patients on their diet or supplements, as well as to quit smoking if patients are smokers seem to be the most viable option. Patients should be well-informed of all the possible options to treat or delay the progression of their disease, including lifestyle changes. If feasible, most patients will be most willing to make these changes in order to preserve their vision, as through a survey, loss of sight is the sense that people in the UK fear losing the most[207]. Moreover, the intake of antioxidants is also beneficial to the human body in general, not only to the eye, therefore it is unlikely that it will do any harm to the patient unless the patient has other systemic conditions, which he or she should seek medical advice before

consuming such supplements. As a result, it is important that AMD patients are being advised about the importance of diet.

To date, there are only a few, if not limited studies that evaluate the nutritional and smoking advice that are provided to patients with or at risk of AMD. The most recent study was conducted by Martin and Lene[208] whereby 371 optometrists and ophthalmologists were questioned on the use of nutritional supplements, changes in diet or smoking cessation to patients who are at risk or with signs of AMD in Sweden. From this study, it was found that optometrists were more likely than ophthalmologists to recommend nutritional supplements in AMD patients and they also provided significantly more advice about diet than the ophthalmologists. On the other hand, ophthalmologists use the AREDS as reference when recommending nutritional supplements and they tend to advice smoking cessation more than optometrists.

In another study conducted in the UK [209] on 1468 optometrists and ophthalmologists, it was found that 67.9% of the respondents frequently provide dietary advice to patients with established AMD and 53.6% of the respondents frequently provide dietary advice to patients who are at risk of AMD. About 93% of the respondents will recommend supplementation in a patient who has advanced AMD in one eye and early AMD in the other. However, the type of supplement recommended did not comply with the current best research evidence, which is the finding from AREDS. Furthermore, as there are no strict regulations for nutritional supplements in the UK, many supplements to improve eye health is available in the market, even though they have not been tested clinically to be effective. Last but not least, in this study, only one in three optometrists regularly asked their patients on their smoking statuses and/or advised them to quit smoking.

In Australia, a study conducted by Downie and Keller on 283 optometrists highlighted that fewer than half of the respondents routinely asked their patients about smoking status and younger practitioners were significantly ($p < 0.05$) less likely to enquire about patients' smoking behaviours. Almost two-third of respondents indicated routinely counsel their patients about diet, and about half of respondents routinely asked their

patients about nutritional supplement intake, especially if the respondent is a female ($p < 0.05$)[210]. However, another study by Downie et al.[211] on 220 patients indicated that approximately one-third of patients indicated having been routinely questioned about their smoking status, diet and nutritional supplement intake by their optometrist, which was lesser than what the optometrists reported in the previous study. Additionally, approximately 75% of the respondents indicated that they feel comfortable talking with their optometrist about their lifestyle behaviours that include smoking status, diet and nutritional supplement intake.

A survey conducted in Singapore[212] revealed that 66% of practicing optometrists and contact lens practitioners were aware that smoking was a risk factor for AMD, and those who were aware of the negative ocular effects were more than twice as likely to assess the smoking status of their patients, and nearly three times more likely to ask patients to quit smoking. Additionally, among the participants who enquired about their patients' smoking status, 62% advised patients to quit smoking if they were known to be current smokers.

In order to encourage eye care practitioners to advice patients with or at risk of AMD on diet or nutritional supplementations, efforts have been made to make this process easier for them. These include educational intervention in the form of leaflets and prompt cards, as well as a clinical decision-making aid in the form of a flowchart. Both methods have proved to be easy and helpful for optometrists when providing nutritional advice to patients with or at risk of AMD[213,214].

This chapter presented the literature review for this thesis, including the pathogenesis and risk factors (modifiable and non-modifiable) of AMD. Studies that evaluated the effect of antioxidants, carotenoids such as lutein and zeaxanthin and PUFAs were also highlighted. The effect of smoking on AMD was discussed, and nutritional and smoking advice to patients with or at risk of AMD by eye care practitioners around the world was evaluated. In the next chapter, the first study of this thesis, "Nutritional and smoking advice to patients with or at risk of AMD by optometrists in Singapore" will be analysed.

Chapter Three: Nutritional and smoking advice to patients with or at risk of AMD by optometrists in Singapore

3.1 Introduction

Chapters one and two highlighted on the pathogenesis, causes and risk factors of AMD, nutrition and smoking and AMD, as well as nutritional and smoking advice to AMD patients by eye care practitioners. Though the nutritional results may vary, dietary modification and/or nutritional supplementation will remain one of the viable options for patients with or at risk of AMD, especially the atrophic type as there is no treatment available at the moment. In this chapter, full details of the study "Nutritional and smoking advice to patients with or at risk of AMD by Singapore optometrists" will be discussed, including the methods and results. This study is important as it will be the first to be conducted in Singapore and it is also important as the prevalence of smoking in Singapore is higher compared to other countries such as the UK and Sweden who has conducted similar studies. With the projected increasing prevalence of AMD due to the ageing population, understanding the nutritional and smoking advice that are being provided to AMD patients is crucial as it gives an indication as to whether AMD patients are receiving the appropriate information on managing their condition. As optometrists are usually the first to diagnose patients with AMD, therefore this study will explore optometrists' nutritional and smoking advice to patients with or at risk of AMD.

3.2 Methods

This study is conducted using a cross-sectional questionnaire to understand the nutritional and smoking advice that optometrists in Singapore are giving to their patients with or at risk of AMD. A questionnaire is adopted in this study as it is a less expensive method of collecting data from a potentially large number of respondents. Most of the questions in the questionnaire are close-ended as it is easier for respondents to answer, hence increasing the response rate.

Validation of questionnaire

The questionnaire was designed with reference to the one used by Lawrenson and Evans[209] and modified after validating with ten optometrists who are currently practicing in Singapore. Ten optometrists from different practice types (retail optical shops, clinical optical shops, hospitals or eye clinics and teaching institutions) were invited to complete the draft questionnaire and to provide feedback on it either verbally to the principal researcher or indicating on the draft questionnaire. The feedback provided by the optometrists were consolidated and the following key changes were made to the draft questionnaire: 1) to include highest qualification attained in the field of optometry for each participant completing the questionnaire; to determine if there is a difference in nutritional and smoking advice between optometrists with different qualifications, 2) location of current practice; to establish if geographic location will affect the nutritional and smoking advice provided by optometrists, 3) optometric tests that were routinely performed on patients aged 50 and above and number of patients aged 50 and above seen per week; to provide an estimation of the prevalence of AMD in Singapore, 4) images to illustrate Category 1 or 2 AMD and Category 3 or 4 AMD; to assist participants who are not too familiar with the AMD classification system, 5) to provide a range in percentage for each frequency option, for instance, rarely (10% of the time), often (50 to 70% of the time); to allow participants completing the questionnaire to have a clearer idea of the frequency terms, 6) to include serving size options for green leafy vegetables and oily fish; to have a clearer picture of how much optometrists are advising their patients to consume and last but not least, to provide example for oily fish such as salmon.

The demographic information for the final questionnaire include age, gender, number of years practicing as a fully registered optometrist, highest qualification attained in the field of optometry as well as the type and location of practice where they are currently working in.

The final questionnaire (Appendix A) consists of nine sections:

1. Tests routinely performed on patients aged 50 and above (2 questions)
2. Number of AMD patients seen per year (2 questions)
3. Perspective on AMD and nutrition (2 questions)
4. Dietary advice to patients with early (Category 1 or 2) AMD (3 questions)
5. Dietary advice to patients with advanced (Category 3 or 4) AMD (3 questions)
6. Dietary advice to patients considered to be at risk of AMD (3 questions)
7. Smoking and AMD (6 questions)
8. Recommendations on nutritional supplements in patients with established or at risk of developing AMD (5 questions)
9. Confidence level in classifying AMD and providing nutritional advice to patients with or at risk of AMD (7 questions)

In section eight, three case scenarios were simulated to illustrate patients with established or at risk of AMD in order to understand the optometrists' nutritional advice to these patients for each scenario.

In section nine, respondents were requested to complete a section that evaluates their self-efficacy using scales to determine if they are likely to accomplish a task in the future. The items in the section were adapted from the study by Stevens et al.[213] and the items are as follows:

I am confident that I could classify the type of AMD a patient has based on retinal signs.
I am confident that I can advise a patient with AMD on the relationship between AMD and nutrition.
I am confident that I can advise a patient with AMD on what foods to eat that might be beneficial for their condition.
I am confident that I can advise a patient with AMD on the quantities of food that might be beneficial for their eye health.
I am confident that I can advise a patient with AMD on when nutritional supplementation may be beneficial.
I am confident that I can advise a patient with AMD on what supplements to take and what dosage to recommend.
I am confident with talking about nutrition to those at risk of AMD.

For each statement, respondents are required to indicate their confidence level from a scale of 0 to 100; 0 being least confident and 100 being most confident. Further details of this self-efficacy survey can be found in chapter 5.4, section “Evaluation of the flowchart”.

The questionnaire is available in a hardcopy and an online version. The hardcopy questionnaire (Appendix A) together with a return envelope, invitational letter (Appendix B) study information sheet (Appendix C), consent form (Appendix D) and an appendix to illustrate AMD categories (Appendix E) was mailed to 573 fully registered optometrists, with no mention of their names, in December 2017 and they were encouraged to complete the questionnaire before 31 March 2018. The questionnaire was designed to be as anonymous as possible by not including personal data of the participants, and only anonymous data will be used for analysis. Confidentiality was ensured by only allowing the principal researcher to have access to all the data collected, and all data are password-protected. The contact list of the 573 optometrists was obtained from the Optometrists and Opticians Board (OOB). This research study was also being advertised on Singapore Optometric groups on Facebook (Appendix F) and members of the Singapore Optometric Association (SOA) also received an email to participate in this study. The online version of the questionnaire was created using Survey Monkey and the link to the questionnaire https://www.surveymonkey.com/r/AMD_advice was available in the invitational letters (Appendix B), Facebook advertisement (Appendix F) as well as the email that was sent out to the SOA members. Optometrists who received the hardcopy questionnaire could opt to complete the questionnaire online using the link that was in the invitational letter. Optometrists who are in the Singapore Optometric Facebook groups and SOA members were not included in the mailing list to prevent optometrists from receiving the invitation twice. It was also highlighted in the invitational letters and advertisement that they should only complete the questionnaire once.

The study information sheet (Appendix C) for this study contained details of the study and after participants have read and understood the information in the study information

sheet, they will initial on the consent form (Appendix D) and mail it back together with the completed questionnaire. If participants are completing the questionnaire online, there will be a link for the participants to access the study information sheet and they will complete an electronic consent form to acknowledge that they have read and understood the study information sheet before they proceed to complete the questionnaire.

The inclusion criteria for this study are:

• Fully registered optometrist under the Optometrists and Opticians Board (OOB) in Singapore

• Currently practicing in Singapore as an optometrist

The exclusion criteria for this study are:

• Optometrists under provisional registration

• Optometrists currently not practicing in Singapore

3.3 Ethics

This research study has been reviewed and approved by the Aston University Research Ethics Committee (AUREC); Application Number 2010 and approved by the Parkway Independent Ethics Committee (PIEC) based in Singapore; reference number PIEC/2017/004 (Appendix G). Moreover, in order to manage appropriately the ethical issues inherent in this study, it is necessary to put the following additional protections of the research participants in place. They are that: (1) informed consent is required before any information from the optometrists can be analysed; (2) Only the principal researcher has access to the information that the optometrists provided; (3) Only anonymous data will be used for this research study.

3.4 Results

32 completed hardcopy questionnaires were mailed back and the responses of these hardcopies were entered manually into the Survey Monkey database by the principal researcher. This equates the response rate of the hardcopies to be 5.6%.

The online version of the questionnaire was created with Survey Monkey (an online survey platform that is cloud-based) and the link was circulated to optometrists who are members of the Singapore Optometric Association (180 members) as well as the Facebook Group, SG OPTOMS (399 members). SOA members who were also members of the SG OPTOMS Facebook group were taken into consideration to ensure there is no duplication. There is a total of 217 (complete and partial) responses via the Survey Monkey link, and 111 were complete (response rate of 19.2%). However, only 141 responses, inclusive of the 32 hardcopy responses will be analysed in this study as 2 respondents indicated that they are not fully registered optometrists. The total number of fully registered optometrists in Singapore is 776 when this questionnaire was disseminated; therefore approximately 18.2% of fully registered optometrists responded.

Demographics of respondents

The mean age of the respondents is 32.1 years; minimum age of 21 and maximum age of 71, with a standard deviation of 7.9. 96 (68.1%) of the respondents are female and 45 (31.9%) are male. The average number of years practicing as a fully registered optometrist is 9.3 years, standard deviation of 7.2 years. The number of respondents with less than or twelve years of experience is 88, and 53 of them have more than twelve years of experience.

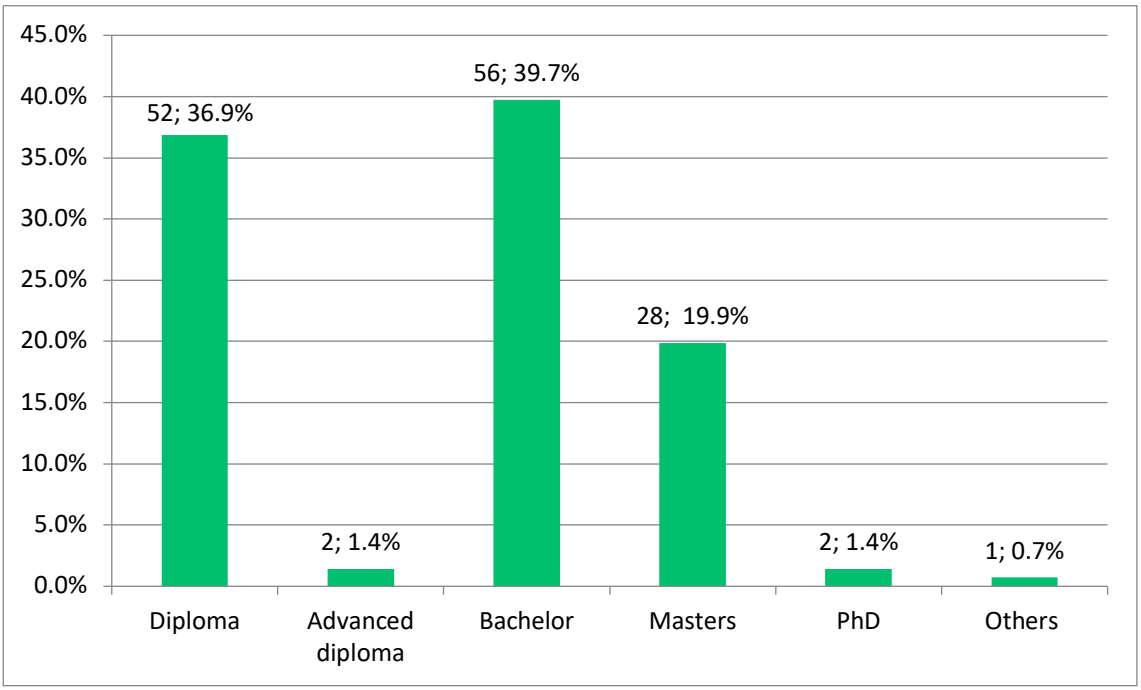

Figure 3.1 : Respondents' highest qualification attained in the field of optometry

Most of the respondents have a Bachelor or Diploma in Optometry and there was one optometrist who graduated in Chinese Medicine Ophthalmology.

Optometrists in Singapore can be working in different practices: 1) retail optical shop whereby optometrists mainly check subjective refraction and anterior ocular health as patients usually go to them for vision correction, such as to purchase glasses or contact lenses. Therefore optometrists working in retail optical shops generally do not routinely perform comprehensive eye examinations on all patients. 2) Clinical optical shop is a practice whereby optometrists will perform a comprehensive eye examination on all patients even though the location and setting is similar to that of a retail optical shop. 3) Hospitals and eye clinics are places where optometrists will perform optometric tests as requested by the ophthalmologists.

The table below represents the type of practices of the respondents.

	Independent/ Private	Chain	Government	Total- N (%)
Retail optical shop	38 (26.6%)	17 (11.9%)	1 (0.7%)	56 (39.2)
Clinical optical shop*	26 (18.2%)	2 (1.4%)	2 (1.4%)	30 (21.0)
Clinical (Includes hospitals and eye clinics)	27 (18.8%)	0	30 (21.0%)	57 (39.8)
				143

*A practice is defined as clinical optical shop if slit-lamp examination and ophthalmoscopy are routinely performed on all patients/customers.

Table 3.1: Respondents' type of current practice (total is 143 as 2 respondents are working in more than one practice)

Based on the data provided by OOB, the percentage of optometrists holding an active practicing certificate and working in retail setting is approximately 60%, and this matches closely to our respondents working in retail and clinical optical shops (60.2%).

	Shopping malls	Neighbour- hood areas	Hospitals	Eye clinics	Institutions (Schools)	Total- N (%)
North	6 (4.3%)	9 (6.4%)	4 (2.8%)	3 (2.1%)	0	22 (15.6)
South	3 (2.1%)	0	2 (1.4%)	0	1 (0.7%)	6 (4.3)
East	8 (5.7%)	10 (7.1%)	0	0	0	18 (12.8)
West	4 (2.8%)	8 (5.7%)	5 (3.5%)	1 (0.7%)	15 (10.6%)	33 (23.4)
Central	26 (18.4%)	6 (4.3%)	11 (7.8%)	19 (13.5%)	0	62 (44.0)
	47	**33**	**22**	**23**	**16**	**141**

Table 3.2: Respondents' location of current practice

The average number of patients aged 50 years and above seen in the respondents' practice per week is 43.9. The average number of patients seen with Category 1 or 2 AMD per year is 77.5 and the average number of patients seen with Category 3 or 4 AMD per year is 19. Based on the numbers reported by the respondents above, the estimated prevalence of Category 1 or 2 AMD is 3.4% and Category 3 or 4 AMD is 0.8%, whereas the report by Cheung et al. states that the prevalence of early AMD in Singapore is 5.1% and late AMD is 0.5%[37].

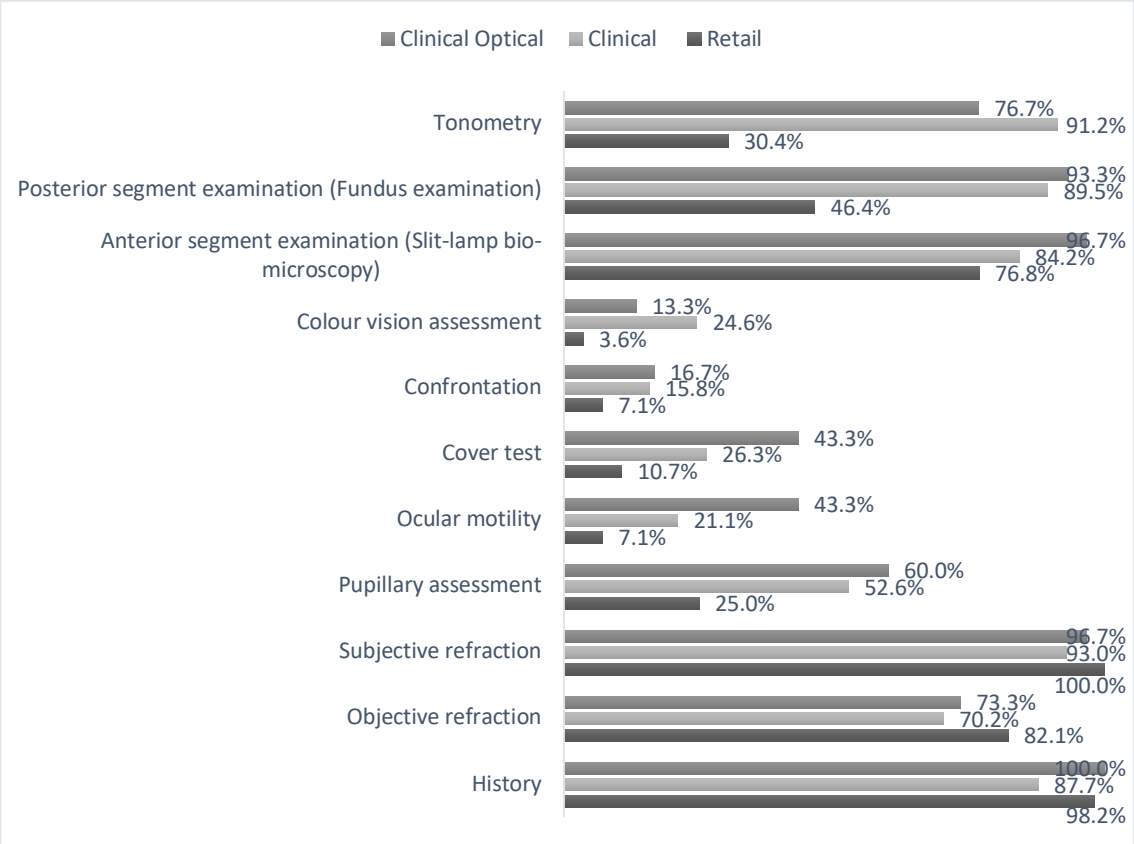

Figure 3.2: Tests routinely performed by respondents on patients aged 50 and above

The respondents added the other tests that are routinely performed on patients aged 50 and above are OCT macular scan, Amsler chart, low vision evaluation and management, corneal topography and fundus photography. 46.4% of optometrists in retail optical shops routinely perform fundus examination on patients aged 50 and above, while 93.3% of optometrists in clinical optical shops routinely perform fundus examination.

137 (97.2%) respondents are aware of the link between AMD and nutrition, and the nutritional advice to patients with or at risk of AMD is restricted for 31 (22.0%) respondents. Respondents working in eye hospitals or clinics can be restricted in terms of giving certain nutritional advice to their AMD patients as the ophthalmologists might prefer to provide such advice themselves, or, would want the optometrists to provide nutritional advice which they believe in. As some retail or clinical optical shops are selling a particular product or supplement in the shop, that could also pose a restriction to optometrists when providing nutritional advice to their patients.

Frequency of dietary advice for patients/customers with early (Category 1 or 2) AMD

	N (%)- Retail	N (%)- Clinical*	N (%)- Total
Never	8 (14.3)	4 (4.7)	12 (8.5)
Rarely (10% of the time)	8 (14.3)	7 (8.2)	15 (10.6)
Sometimes/ Often (20-70% of the time)	21 (37.5)	33 (38.8)	54 (38.3)
Most of the time/ Always (80-100% of the time)	19 (33.9)	41 (48.2)	60 (42.6)

Table 3.3: Frequency of dietary advice for patients/customers with early (Category 1 or 2) AMD
*Clinical includes clinical optical shops, eye clinics and hospitals

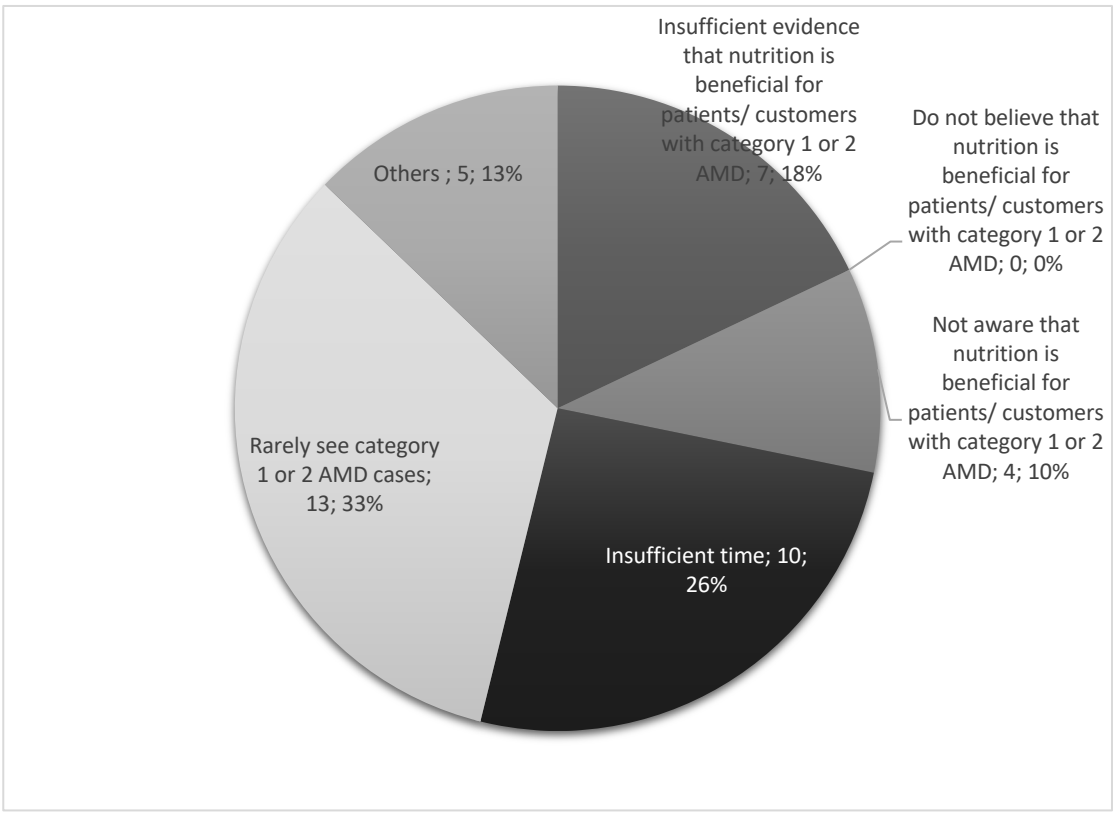

Figure 3.3: Main reason(s) for not/rarely advising dietary advice for patients/customers with early (Category 1 or 2) AMD

27 respondents indicated that they rarely or do not provide dietary advice to patients with early AMD and when asked to indicate their reasons for not doing so, they were able to select more than one option from the list provided, as shown in figure 3.3.

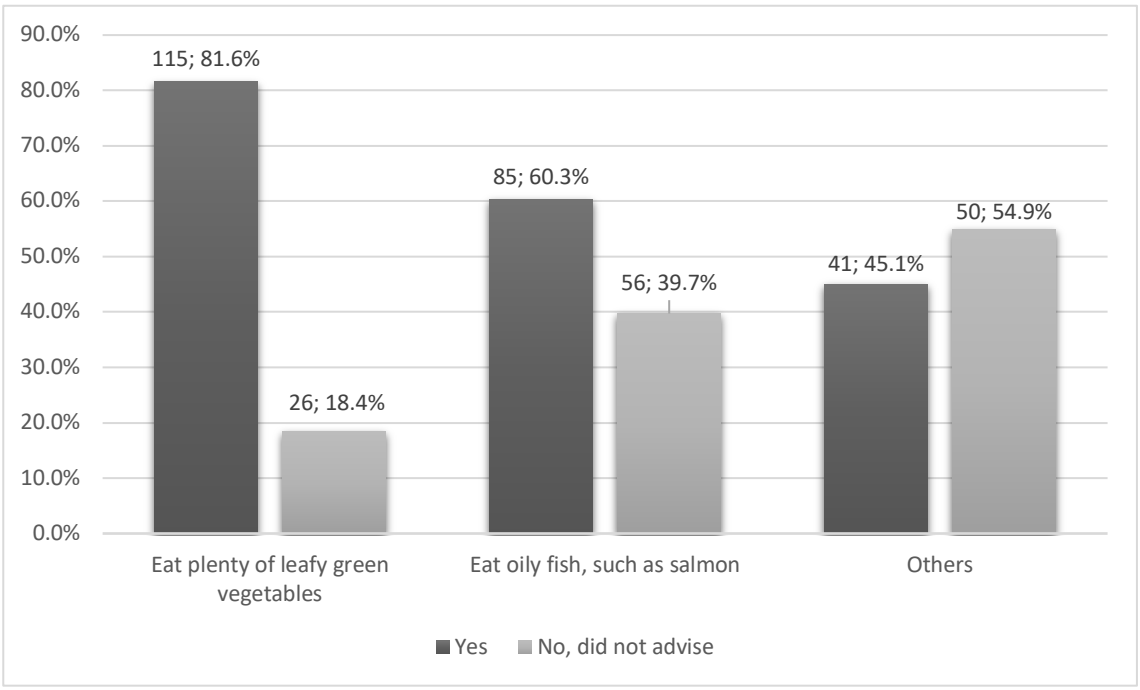

Figure 3.4: Advice to consume leafy green vegetables, oily fish or other foods for patients/customers with early (Category 1 or 2) AMD

80 (56.7%) of the respondents advised their patients with early AMD to consume both leafy green vegetables and oily fish.

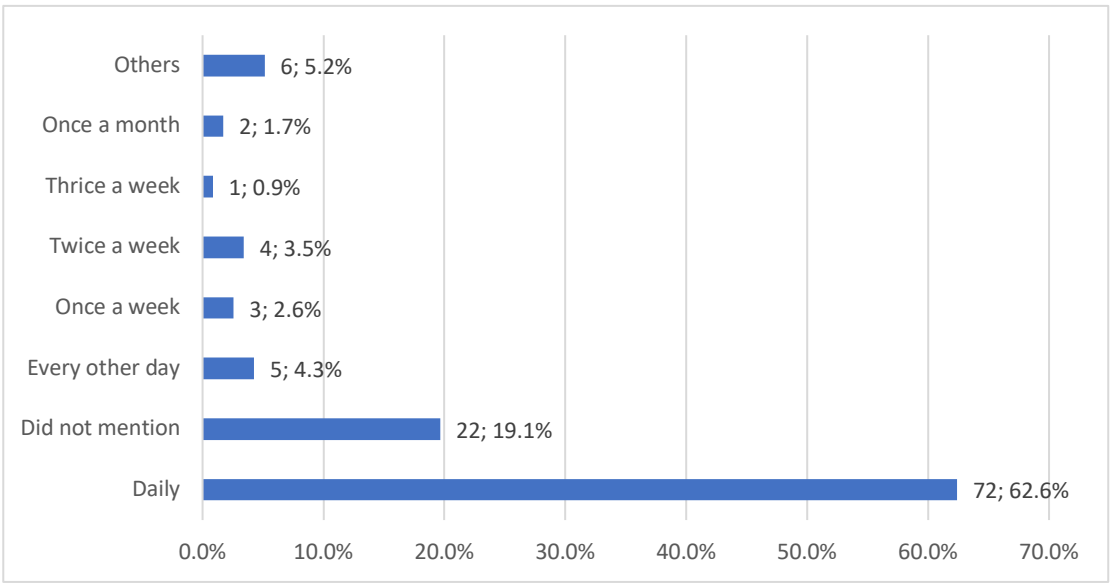

Figure 3.5: Frequency to consume green leafy vegetables to patients/customers with Category 1 or 2 AMD (n=115)

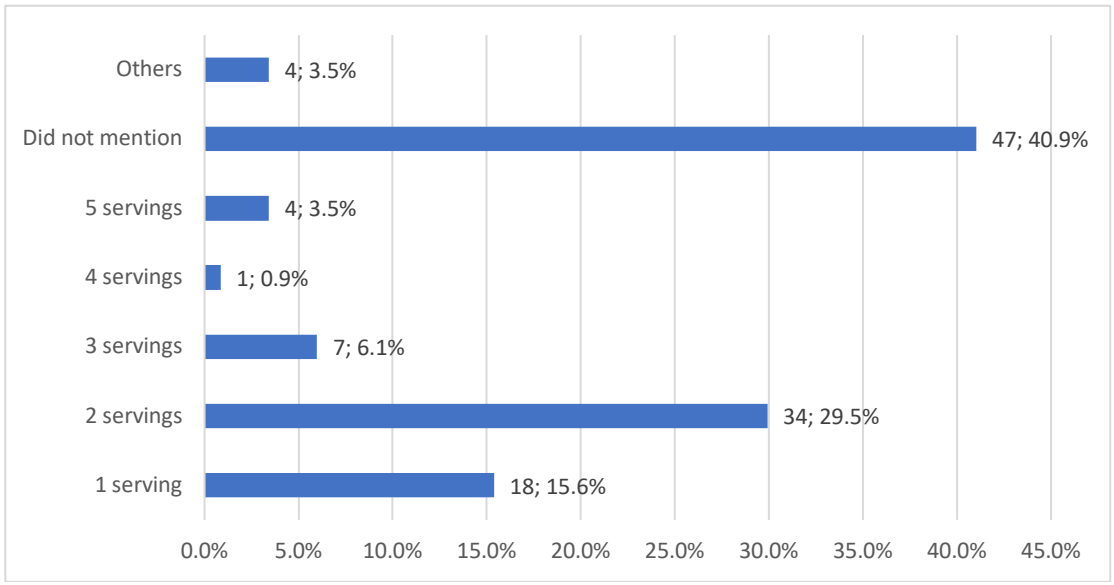

Figure 3.6: Amount of green leafy vegetables to consume for patients/consumers with Category 1 or 2 AMD (n=115)

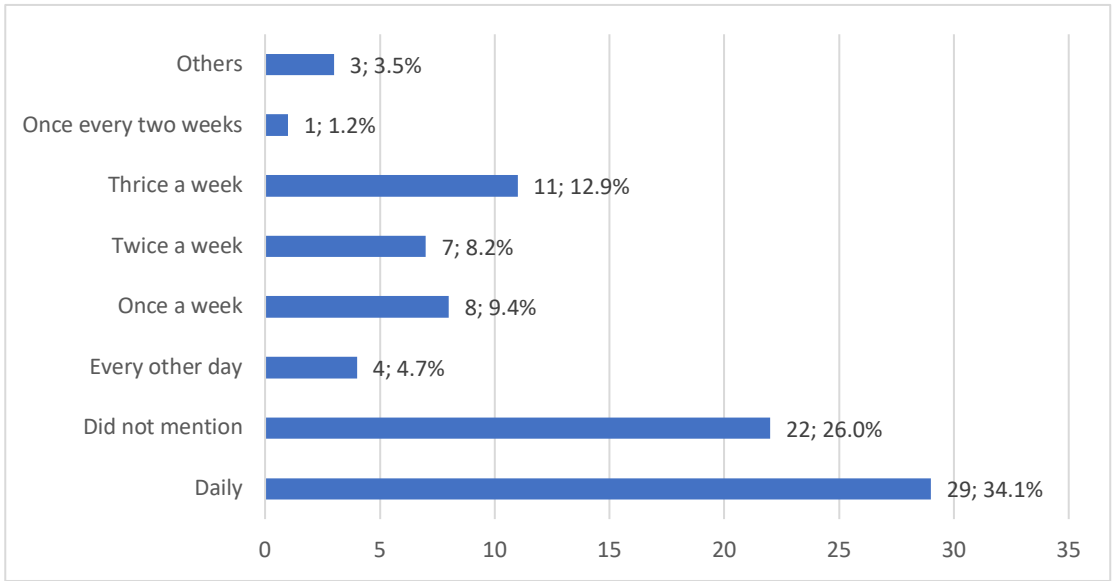

Figure 3.7: Frequency to consume oily fish to patients/customers with Category 1 or 2 AMD (n=85)

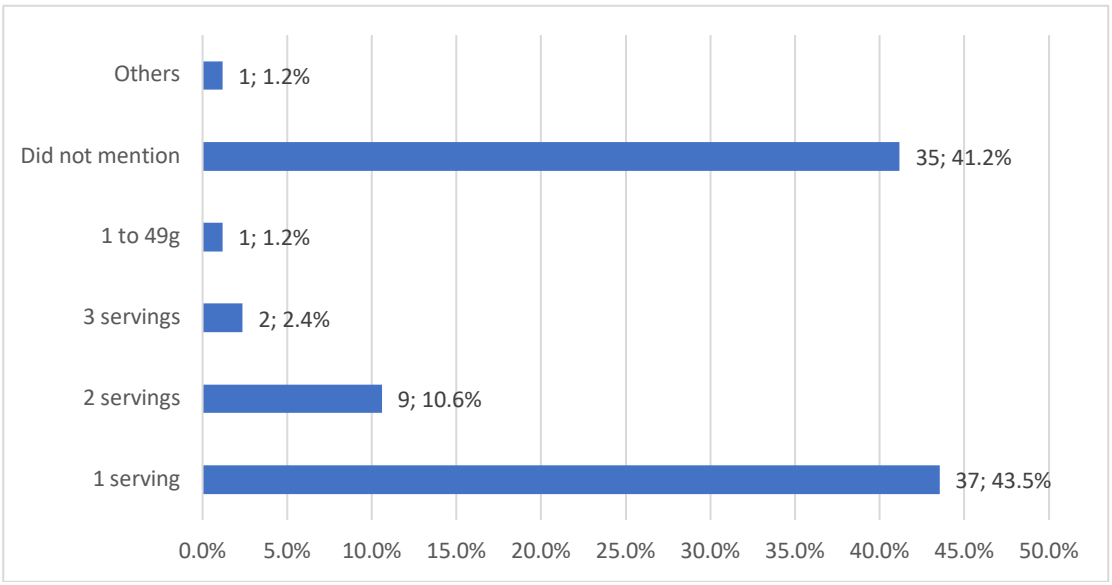

Figure 3.8: Amount of oily fish to consume for patients/consumers with Category 1 or 2 AMD (n=85)

134 (95.0%) respondents think that optometrists in Singapore should be providing dietary advice to patients or customers with early (Category 1 or 2) AMD. The optometrists who indicated that they should not be providing dietary advice to patient or customers with early AMD is because 1) they feel that they can give as general advice, but not for main advice to prevent or treat AMD; 2) they are not trained to provide such advice; 3) there is no evidence to show that it helps, therefore perhaps to provide dietary advice to all patients, including healthy ones; 4) it is not optical related.

Frequency of dietary advice for patients/customers with advanced (Category 3 or 4) AMD

	N (%)- Retail	N (%)- Clinical	N (%)- Total
Never	10 (17.9)	8 (9.4)	18 (12.8)
Rarely (10% of the time)	11 (19.6)	8 (9.4)	19 (13.5)
Sometimes/ Often (20-70% of the time)	13 (23.2)	24 (28.2)	37 (26.2)
Most of the time/ Always (80-100% of the time)	22 (39.3)	45 (52.9)	67 (47.5)

Table 3.4: Frequency of dietary advice for patients/customers with advanced (Category 3 or 4) AMD

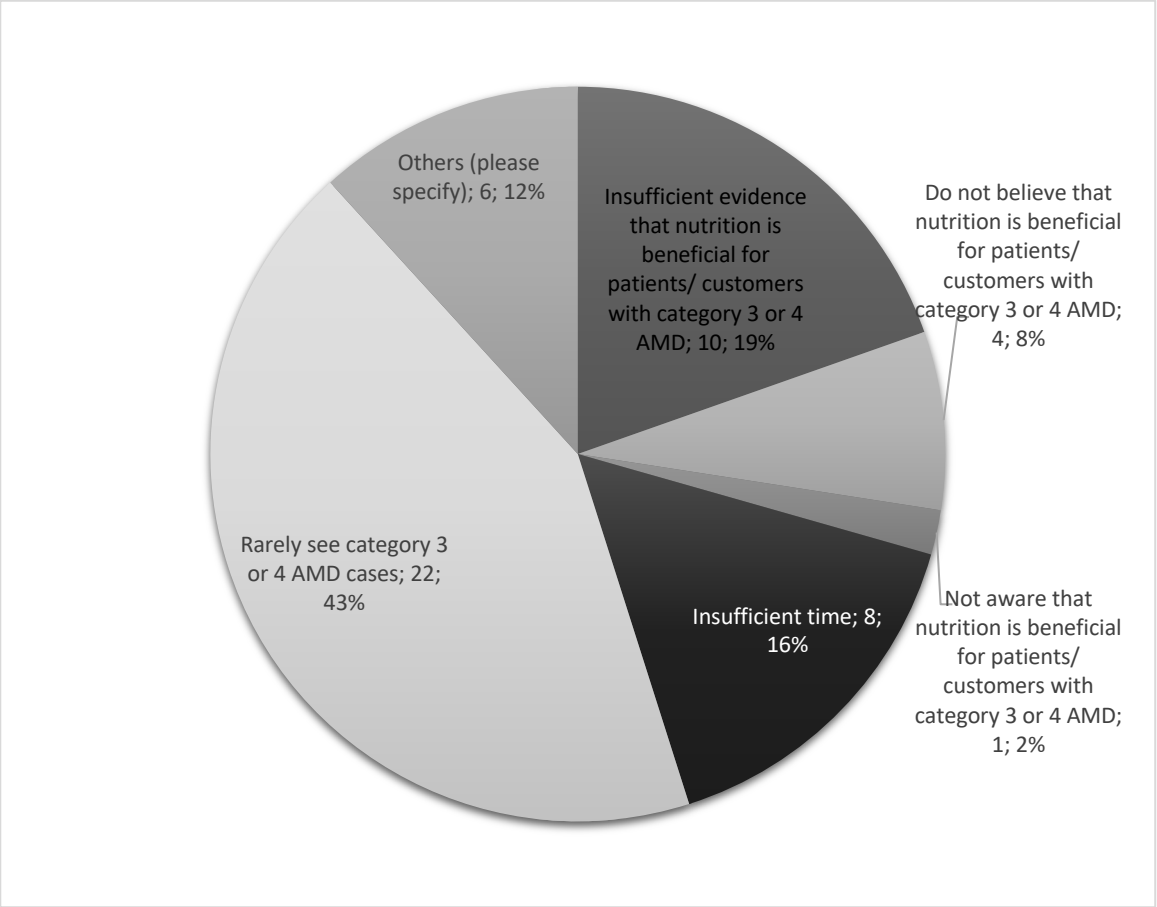

Figure 3.9: Main reason(s) for not/rarely advising dietary advice for patients/customers with advanced (Category 3 or 4) AMD

37 respondents indicated that they rarely or do not provide dietary advice to patients with advanced AMD and when asked to indicate their reasons for not doing so, they were able to select more than one option from the list provided, as shown in figure 3.9. The other reasons highlighted by the respondents are patients with advanced AMD are usually managed by ophthalmologists, hence they will know the food that are beneficial for their condition.

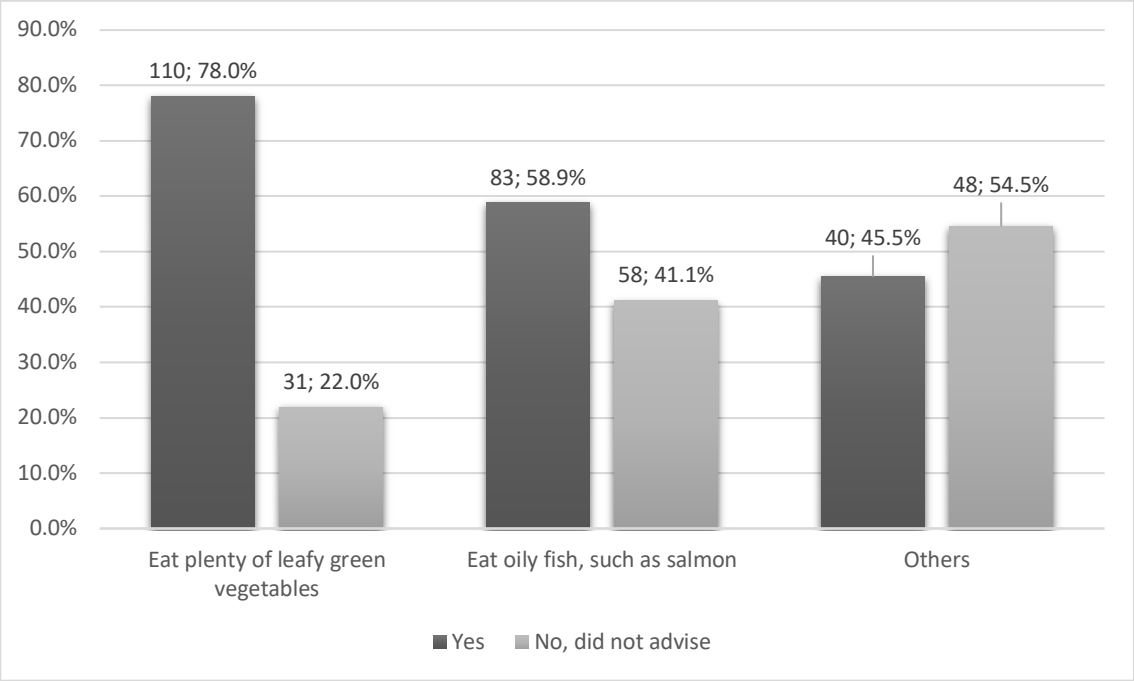

Figure 3.10: Advice to consume leafy green vegetables, oily fish or other foods for patients/customers with advanced (Category 3 or 4) AMD

58.9% of the respondents in this study advised patients with advanced AMD to consume both green leafy vegetables and oily fish.

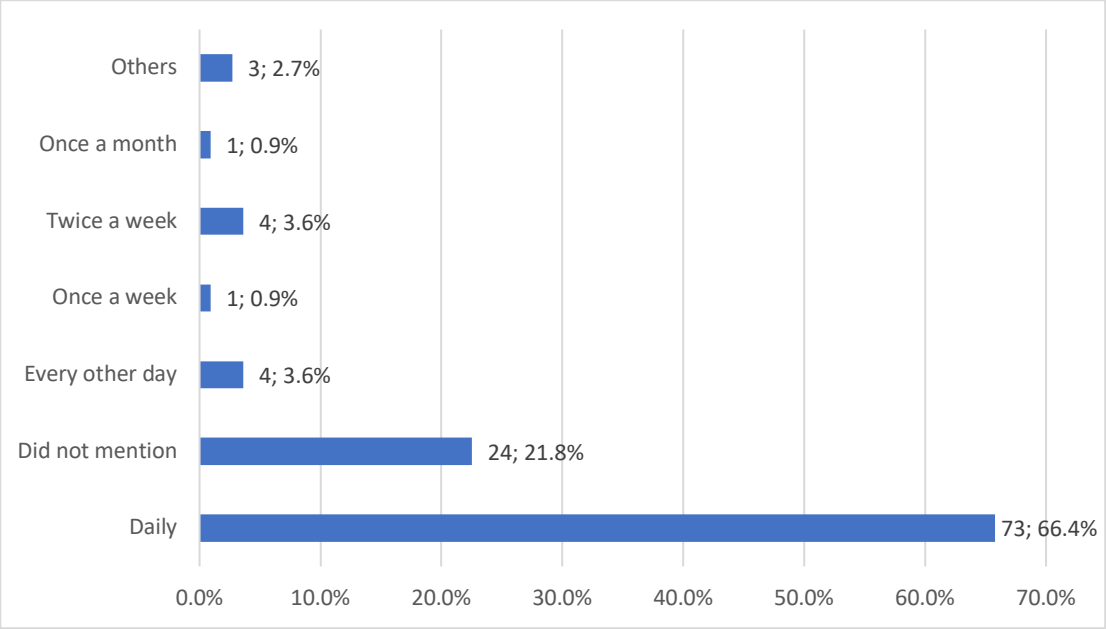

Figure 3.11: Frequency to consume green leafy vegetables to patients/customers with advanced (category 3 or 4) AMD (n=110)

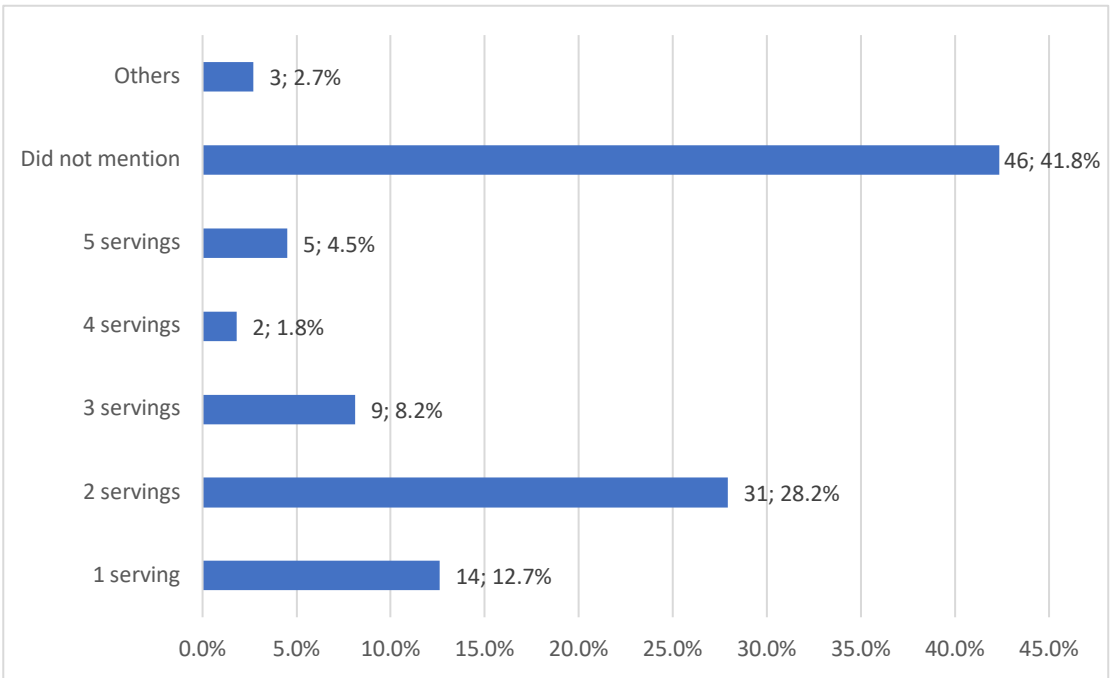

Figure 3.12: Amount of green leafy vegetables to consume for patients/consumers with advanced (Category 3 or 4) AMD (n=110)

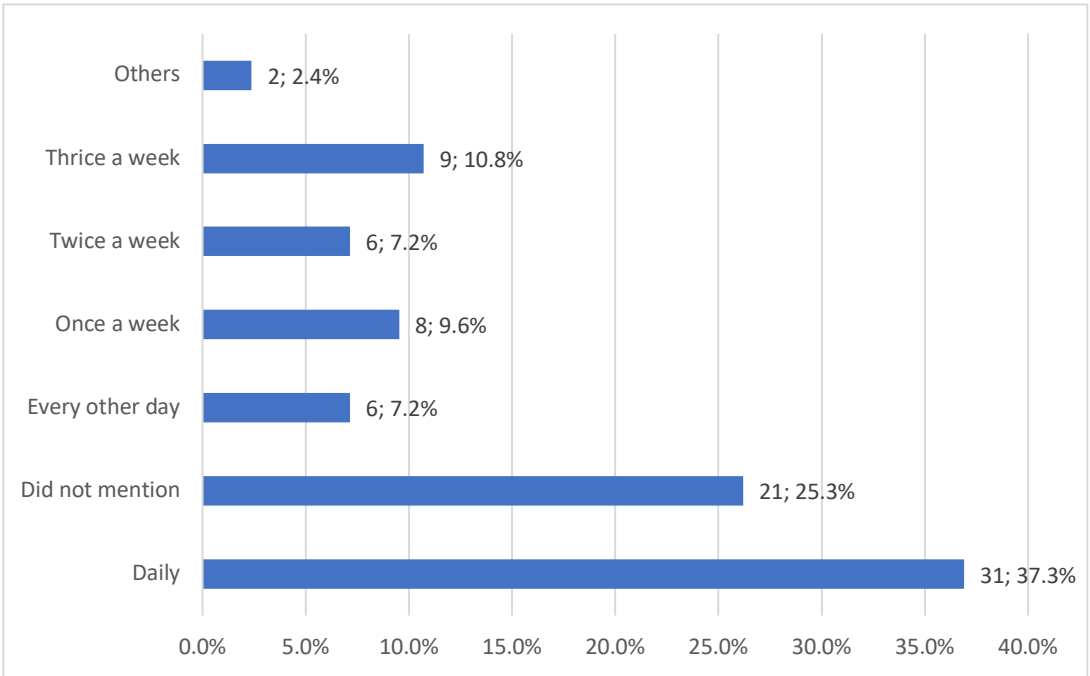

Figure 3.13: Frequency to consume oily fish to patients/customers with advanced (Category 3 or 4) AMD (n=83)

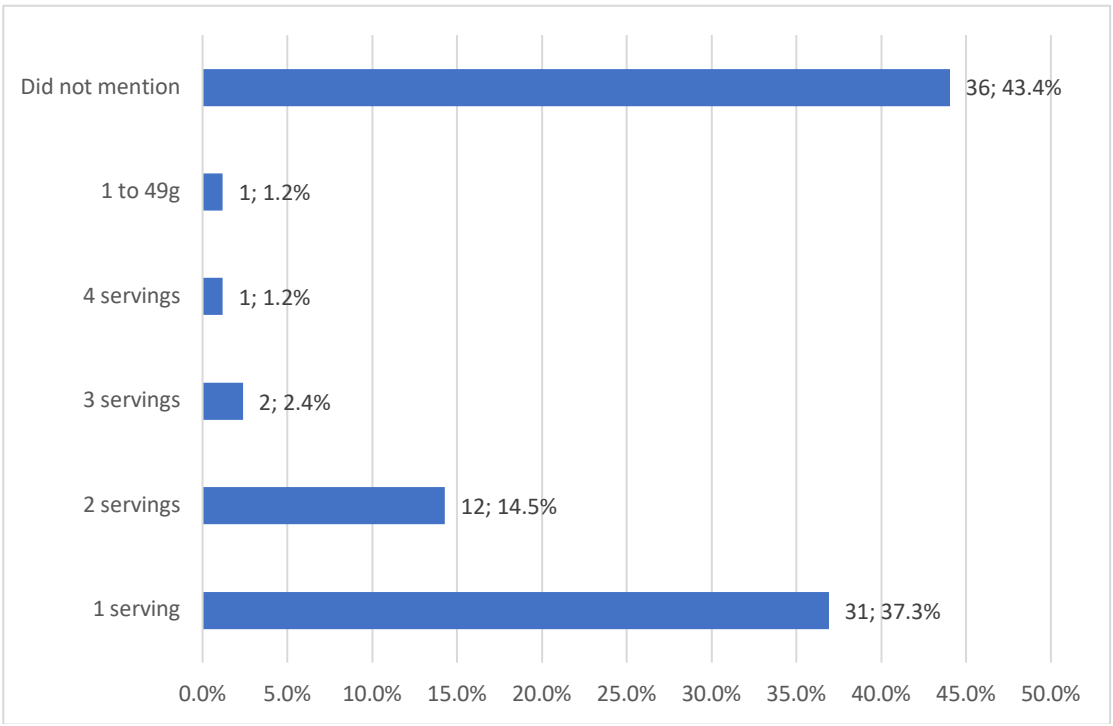

Figure 3.14: Amount of oily fish to consume for patients/consumers with advanced (Category 3 or 4) AMD (n=83)

130 (92.20%) respondents think that optometrists in Singapore should be providing dietary advice to patients/customers with advanced (Category 3 or 4) AMD. The main reasons for not advising is that optometrists feel that advanced (Category 3 or 4) AMD should be managed by an ophthalmologist, including dietary advice, and optometrists are not professionally trained in this area, hence their advice might contradict the ophthalmologist's advice. However, one optometrist mentioned that he or she can provide advice as general recommendation and not as a main advice for treatment, and one optometrist highlighted that "dietary advice may not be of much use in such patients".

Frequency of dietary advice for patients/customers considered to be at risk of AMD

	N (%)- Retail	N (%)- Clinical	N (%)- Total
Never	12 (21.4)	9 (10.6)	21 (14.9)
Rarely (10% of the time)	6 (10.7)	10 (11.8)	16 (11.3)
Sometimes/ Often (20-70% of the time)	21 (37.5)	39 (45.9)	60 (42.6)
Most of the time/ Always (80-100% of the time)	17 (30.4)	27 (31.7)	44 (31.2)

Table 3.5: Frequency of dietary advice for patients/customers considered to be at risk of AMD

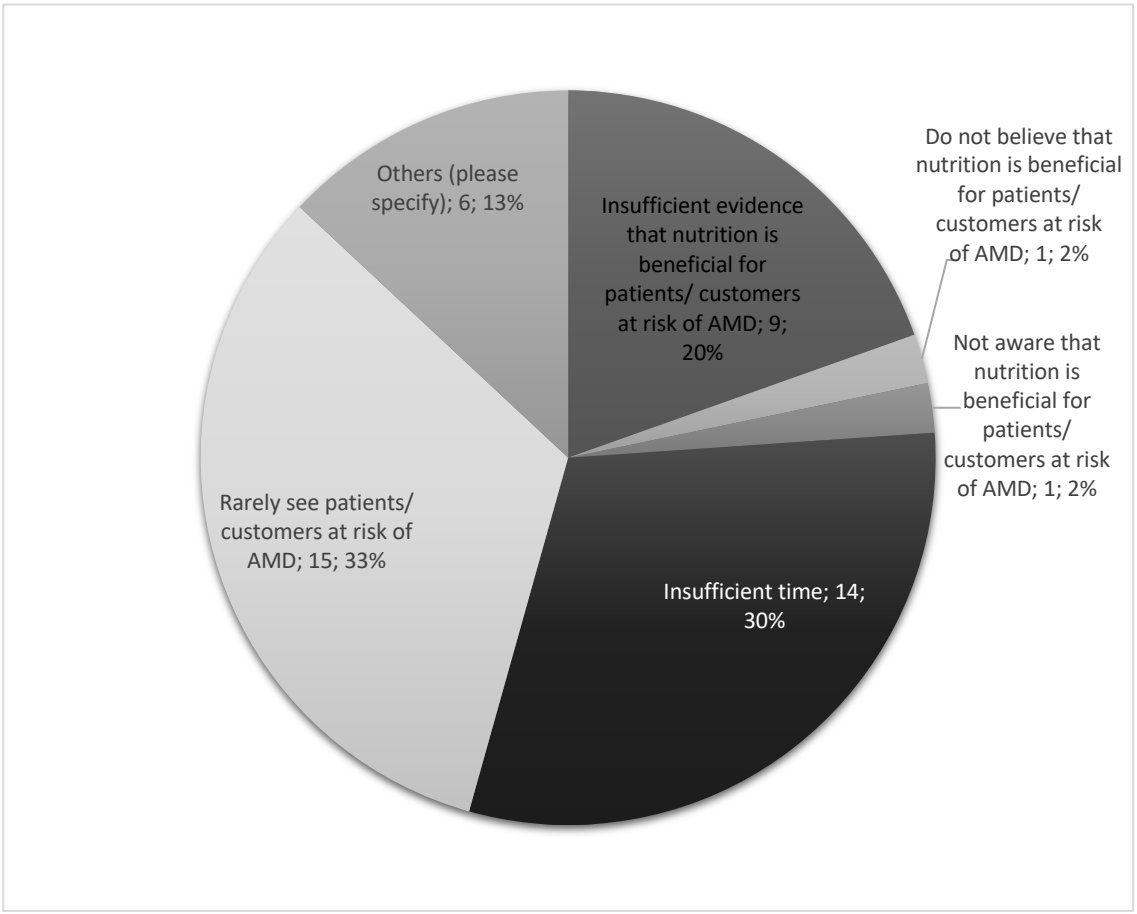

Figure 3.15: Main reason(s) for not/rarely advising dietary advice for patients/customers considered to be at risk of AMD

37 respondents indicated that they rarely or do not provide dietary advice to patients considered to be at risk of AMD and when asked to indicate their reasons for not doing

so, they were able to select more than one option from the list provided, as shown in figure 3.15.

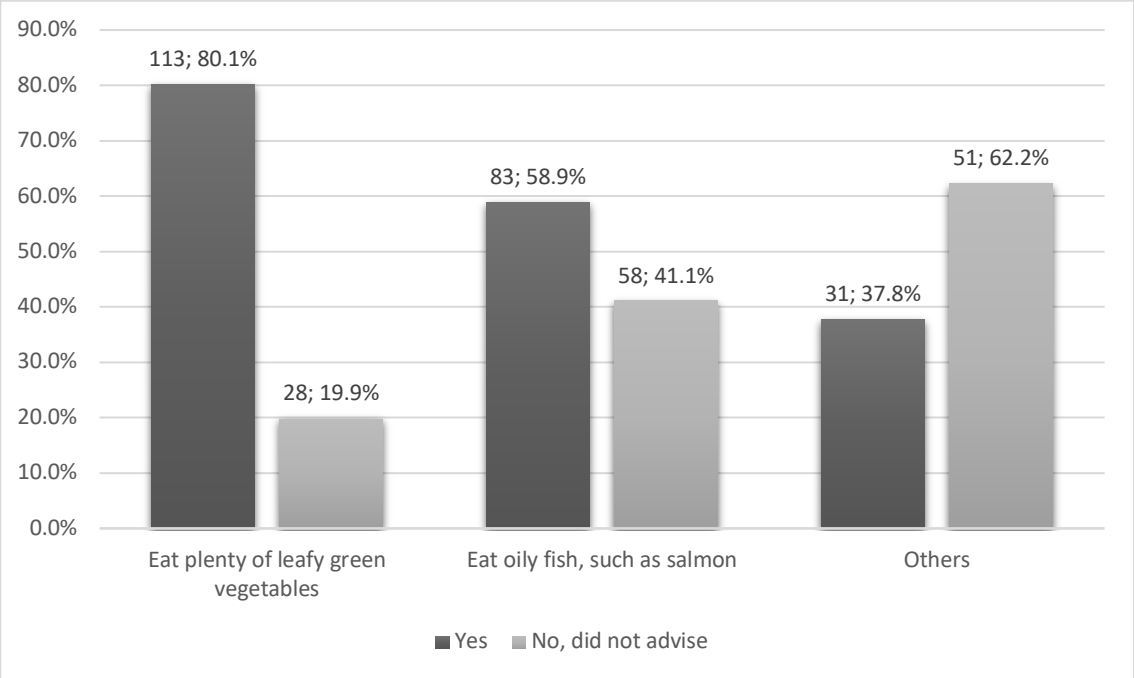

Figure 3.16: Advice to consume leafy green vegetables, oily fish or other foods for patients/customers considered to be at risk of AMD

81 (57.4%) respondents in this study advised patients at risk of AMD to consume both green leafy vegetables and oily fish.

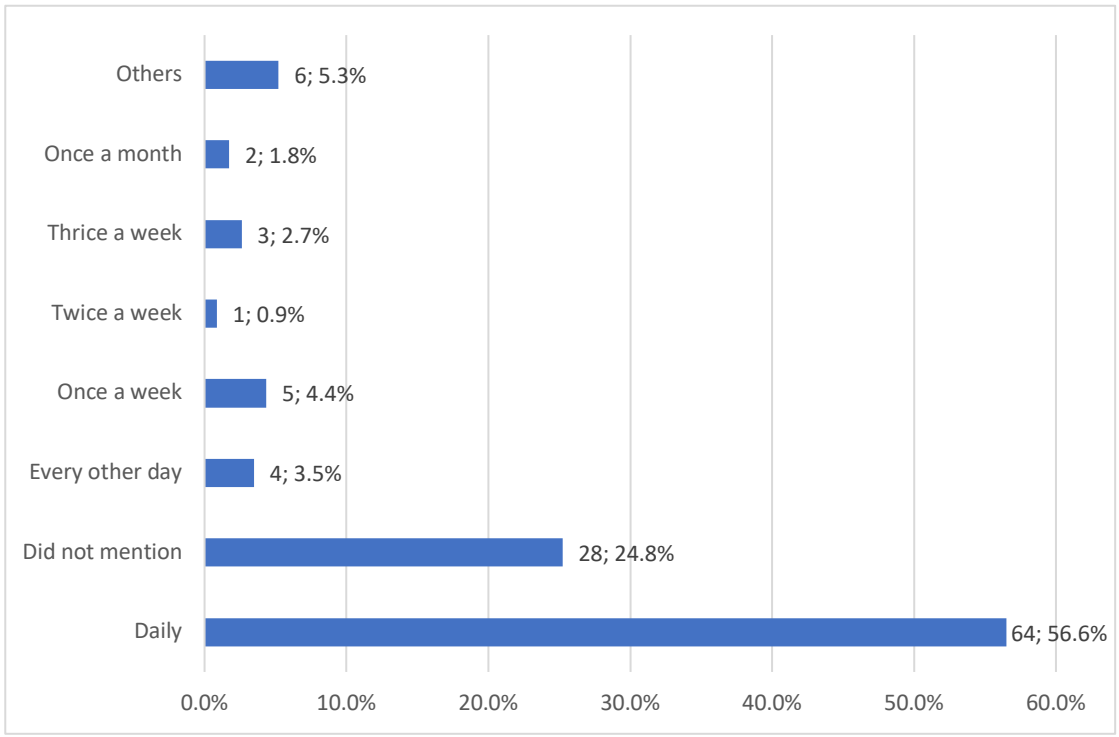

Figure 3.17: Frequency to consume green leafy vegetables to patients/customers considered to be at risk of AMD (n=113)

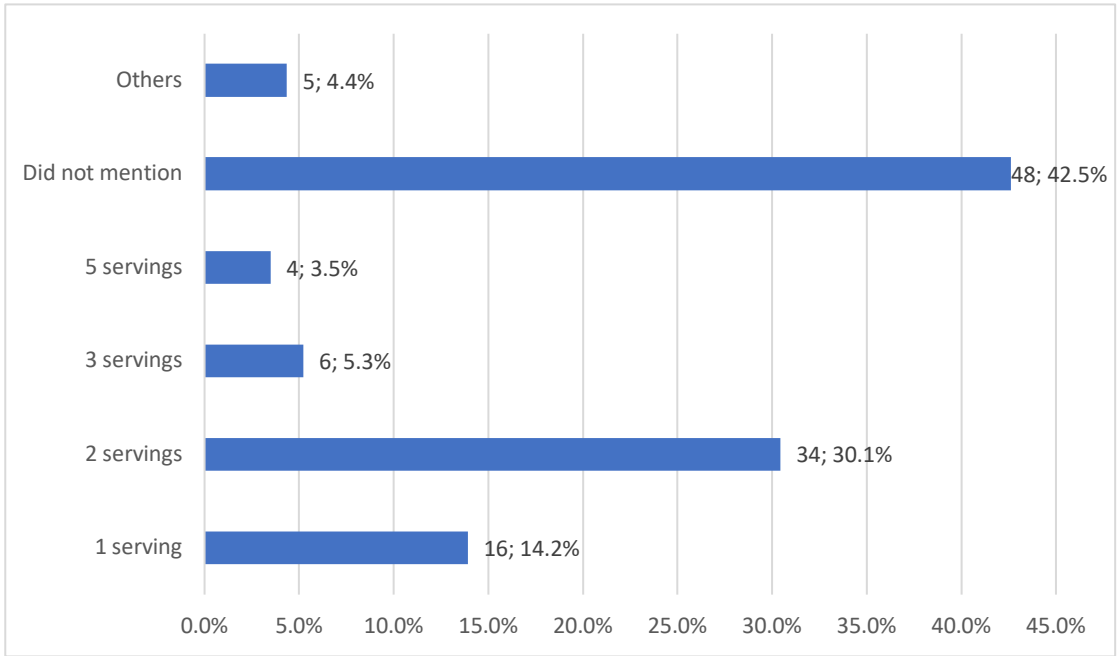

Figure 3.18: Amount of green leafy vegetables to consume for patients/consumers considered to be at risk of AMD (n=113)

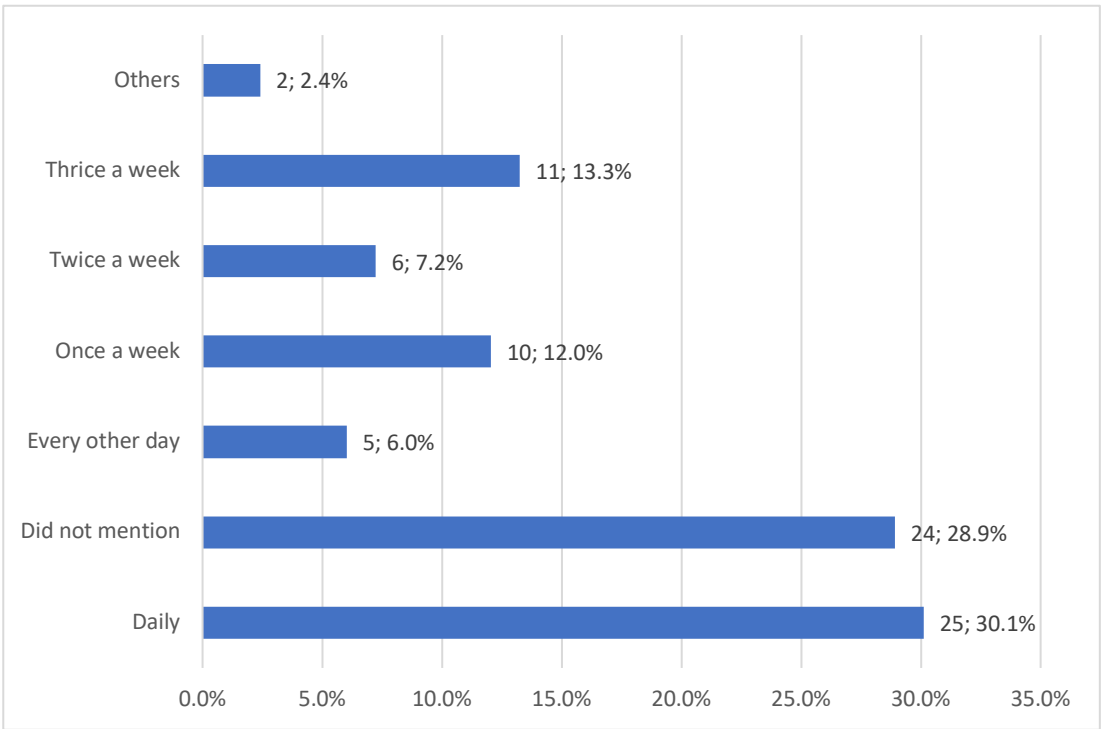

Figure 3.19: Frequency to consume oily fish to patients/customers considered to be at risk of AMD (n=83)

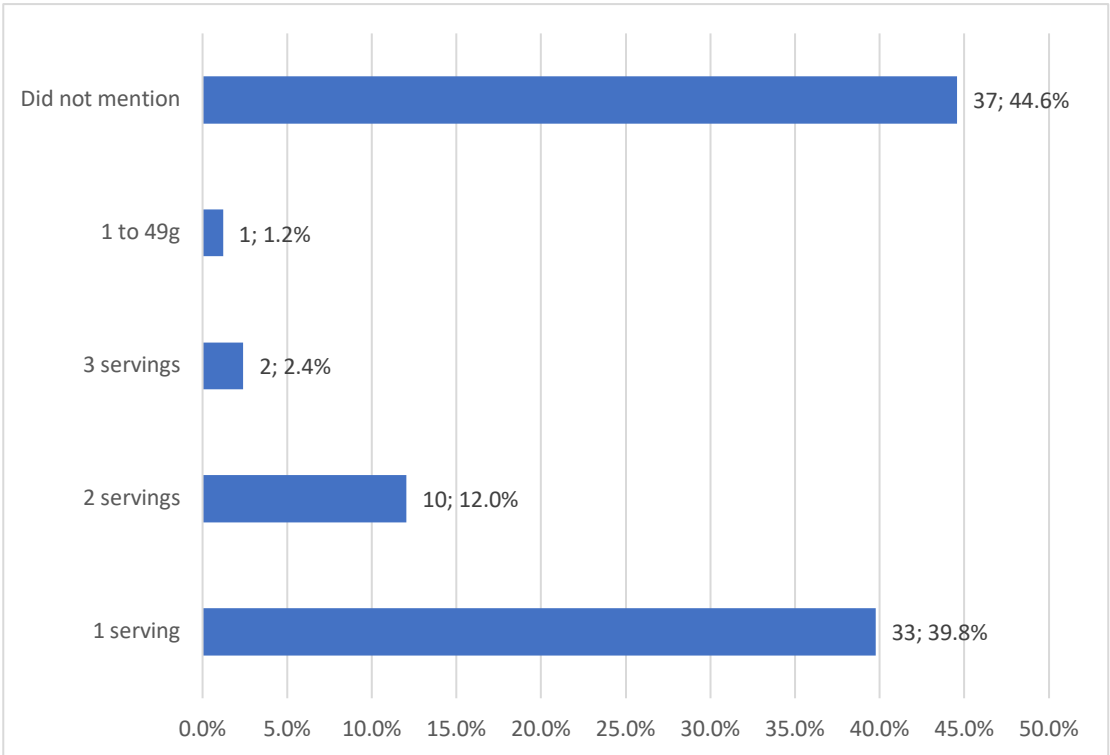

Figure 3.20: Amount of oily fish to consume for patients/consumers considered to be at risk of AMD (n=83)

136 (96.5%) respondents think that optometrists in Singapore should be providing dietary advice to patients/customers considered to be at risk of AMD. The reasons for

not providing dietary advice is that they felt that these patients should see an ophthalmologist, and it is not optical related.

Smoking and AMD

138 (97.87%) respondents are aware that smoking is a risk factor of AMD, and the table below depicts the frequency of taking a smoking history in new or first time patients among the respondents.

	N (%)- Retail	N (%)- Clinical	N (%)- Total	N (%)- UK[209]	N (%)- Sweden[208]
Never/ Rarely (10% of the time)	18 (32.1)	18 (21.2)	36 (25.6)	369 (27.7)	150 (55)
Sometimes/ Often (20-70% of the time)	28 (50.0)	31 (36.5)	59 (41.8)	533 (40.0)	75 (28)
Most of the time/ Always (80-100% of the time)	10 (17.9)	36 (42.3)	46 (32.6)	431 (32.3)	46 (17)

Table 3.6: Frequency of taking a smoking history in new/first time patients/customers

	N (%)- Retail	N (%)- Clinical	N (%)- Total	N (%)- UK[209]
Never/ Rarely (10% of the time)	23 (41.1)	32 (37.6)	55 (39)	474 (35.6)
Sometimes/ Often (20-70% of the time)	27 (48.2)	39 (45.9)	66 (46.8)	576 (43.2)
Most of the time/ Always (80-100% of the time)	6 (10.7)	14 (16.5)	20 (14.2)	283 (21.2)

Table 3.7: Frequency of taking a smoking history in non-first time patients/customers

	N (%)- Retail	N (%)- Clinical	N (%)- Total	N (%)- UK[209]
Never/ Rarely (10% of the time)	17 (30.4)	14 (16.5)	31 (22)	129 (9.7)
Sometimes/ Often (20-70% of the time)	26 (46.4)	40 (47.0)	66 (46.8)	546 (41.0)
Most of the time/ Always (80-100% of the time)	13 (23.2)	31 (36.5)	44 (31.2)	658 (49.4)

Table 3.8: Frequency of informing smokers of the link between smoking and AMD

	N (%)-Retail	N (%)-Clinical	N (%)-Total	N (%)-UK[209]	N (%)-Sweden [208]
Never/ Rarely (10% of the time)	22 (39.3)	12 (14.1)	34 (24.1)	345 (25.9)	164 (61)
Sometimes/ Often (20-70% of the time)	14 (25.0)	27 (31.8)	41 (29.1)	539 (40.8)	53 (20)
Most of the time/ Always (80-100% of the time)	20 (35.7)	46 (54.1)	66 (46.8)	449 (33.7)	51 (19)

Table 3.9: Frequency of advising patients/customers with AMD to stop smoking

	N (%)-Retail	N (%)-Clinical	N (%)-Total
Never/ Rarely (10% of the time)	20 (35.7)	18 (21.2)	38 (26.9)
Sometimes/ Often (20-70% of the time)	19 (33.9)	20 (23.5)	39 (27.7)
Most of the time/ Always (80-100% of the time)	17 (30.4)	47 (55.3)	64 (45.4)

Table 3.10: Frequency of advising patients/customers at risk of AMD to stop smoking

42.3% of the clinical optometrists in Singapore take a smoking history in new or first time patients most of the time, compared with 32.3% of the optometrists in the UK. Almost half of the optometrists in the UK inform smokers of the link between smoking and AMD most of the time but only 36.5% of optometrists in Singapore does the same. Conversely, slightly more than half of the optometrists in Singapore advise AMD patients to stop smoking most of the time and 33.7% of the optometrists in the UK advised AMD patients to stop smoking most of the time.

Nutritional supplements for case scenarios

As mentioned under the methods section, three clinical case scenarios are simulated to understand the type of supplements that are recommended for these patients by the Singapore optometrists, and they are allowed to select more than one option for each scenario. The three case scenarios are the same ones used by Lawrenson and Evans[209] and Martin[208] in their studies to allow comparison between optometrists in the UK, Sweden and Singapore.

Scenario 1: 55 year old patient/ customer with no evidence of AMD but with one or more parents and/or siblings affected by AMD.

66.4% of the respondents in this study would recommend supplements compared to 33.6% in the study by Lawrenson and Evans[209] in the UK and 50.1% in the study by Martin[208] in Sweden.

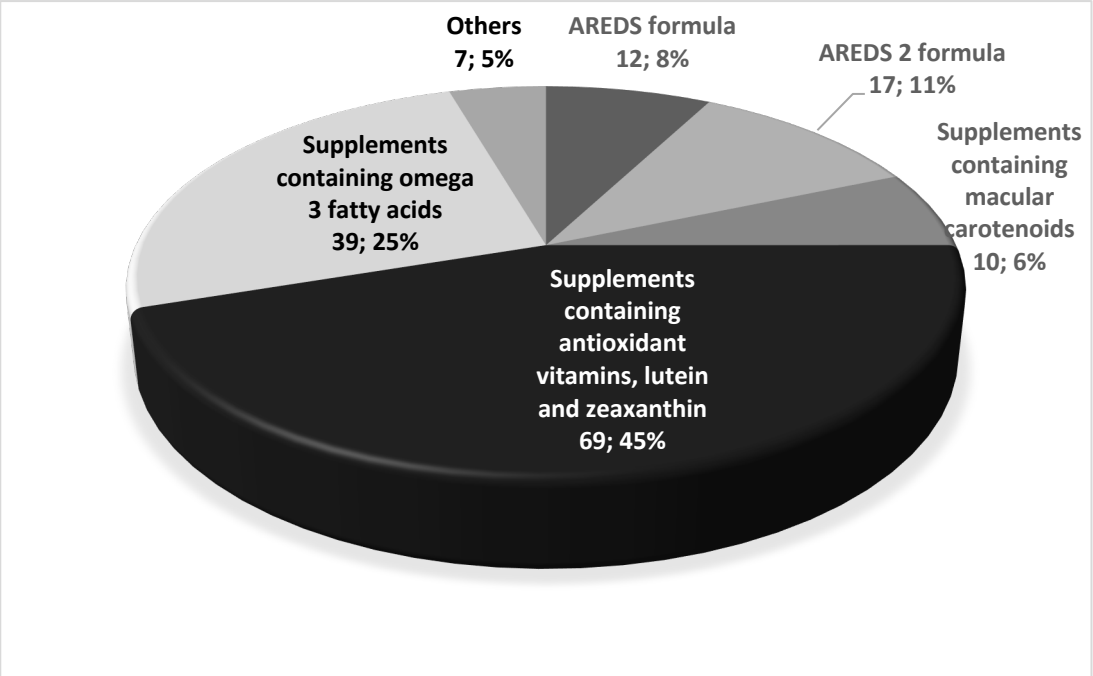

Figure 3.21: Supplements to recommend to patient in Scenario 1 by respondents

Others include regular monitoring with Amsler chart and annual eye examination, eat green leafy vegetables and other foods that are high in lutein or zeaxanthin, to have a diet rich in green leafy vegetables, a healthy lifestyle and cease smoking if patient is a smoker, to take supplements in consultation with a pharmacist or GP, Ocuvite, wolfberries, and to go for eye check annually.

In the UK study[209], 15.6% would recommend an AREDS formula, 62.1% would recommend a supplement containing macular carotenoids, 63.0% would recommend a supplement containing antioxidant vitamins, lutein and zeaxanthin, and 20.1% would recommend a supplement containing omega 3 fatty acids.

Scenario 2: 65 year old patient/ customer with advanced AMD in one eye and early AMD in the other.

92.3% of the respondents would recommend supplements compared to 92.8% in the study by Lawrenson and Evans[209] in the UK and 73.3% in the study by Martin[208] in Sweden.

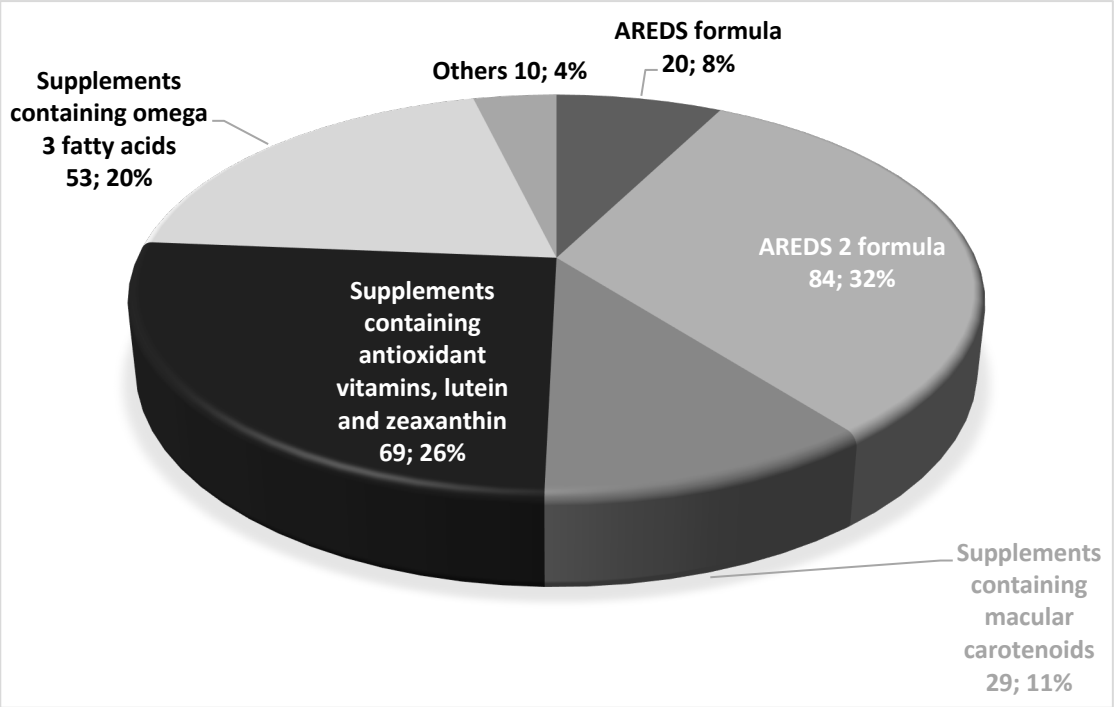

Figure 3.22: Supplements to recommend to patient in Scenario 2 by respondents

Others include regular monitoring with Amsler chart and regular six monthly eye examination, diet with green leafy vegetables, to see an ophthalmologist, to have a diet rich in green leafy vegetables, to have a healthy lifestyle, to cease smoking and AREDS 2 if patient is a smoker, to refer to eye clinic, Ocuvite, wolfberries and TCM herbs.

In the UK study[209], 27.5% would recommend an AREDS formula, 64.6% would recommend a supplement containing macular carotenoids, 57.2% would recommend a supplement containing antioxidant vitamins, lutein and zeaxanthin, and 20.7% would recommend a supplement containing omega 3 fatty acids.

Scenario 3: 75 year old patient/ customer with advanced AMD in both eyes

88.1%% of the respondents would recommend supplements compared to 44.8% in the study by Lawrenson and Evans[209] in the UK and 34.3% in the study by Martin[208] in Sweden.

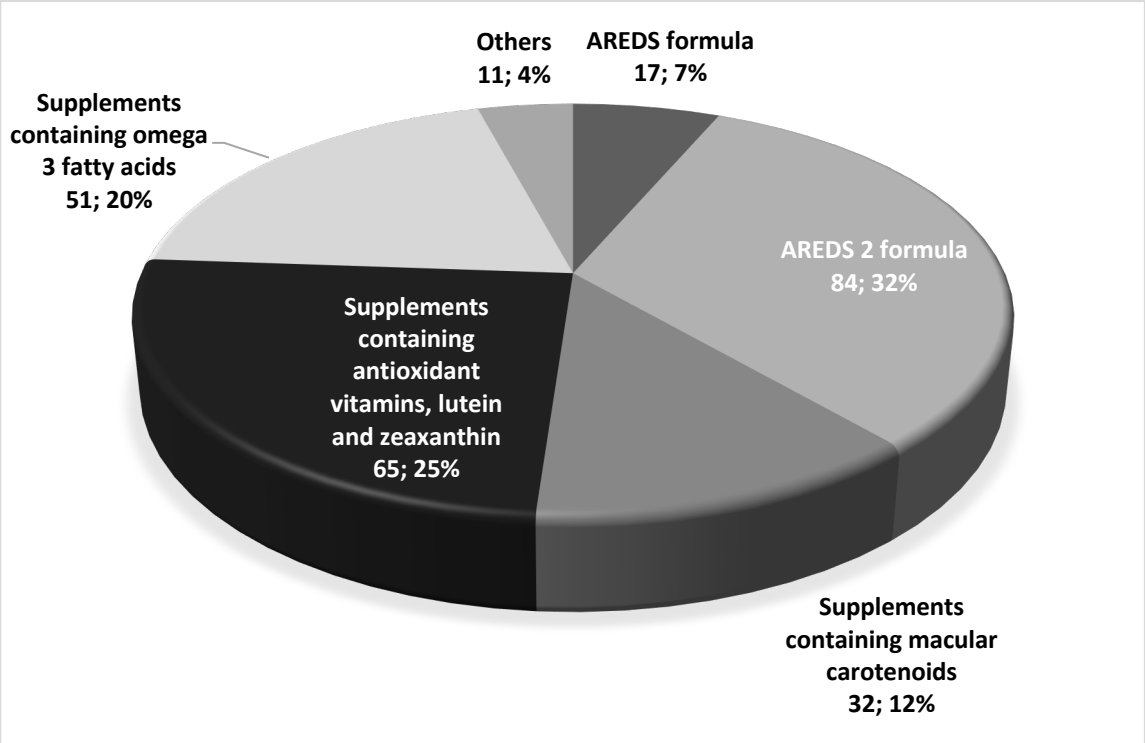

Figure 3.23: Supplements to recommend to patient in Scenario 3 by respondents

Others include regular monitoring with Amsler chart and regular six monthly eye examination, to eat green leafy vegetables, to see an ophthalmologist, to have a healthy lifestyle and cease smoking if patient is a smoker, to refer to eye clinic, Ocuvite, wolfberries and TCM herbs.

In the UK study[209], 26.8% would recommend an AREDS formula, 65.8% would recommend a supplement containing macular carotenoids, 56.7% would recommend a supplement containing antioxidant vitamins, lutein and zeaxanthin, and 25.0% would recommend a supplement containing omega 3 fatty acids.

111 (78.72%) of the respondents would consider the smoking status or history of their patients when recommending nutritional supplements. The figure below shows the sources of evidence that respondents use and others include ophthalmologist whom the optometrist is working for, Google, Wikipedia and sales representative.

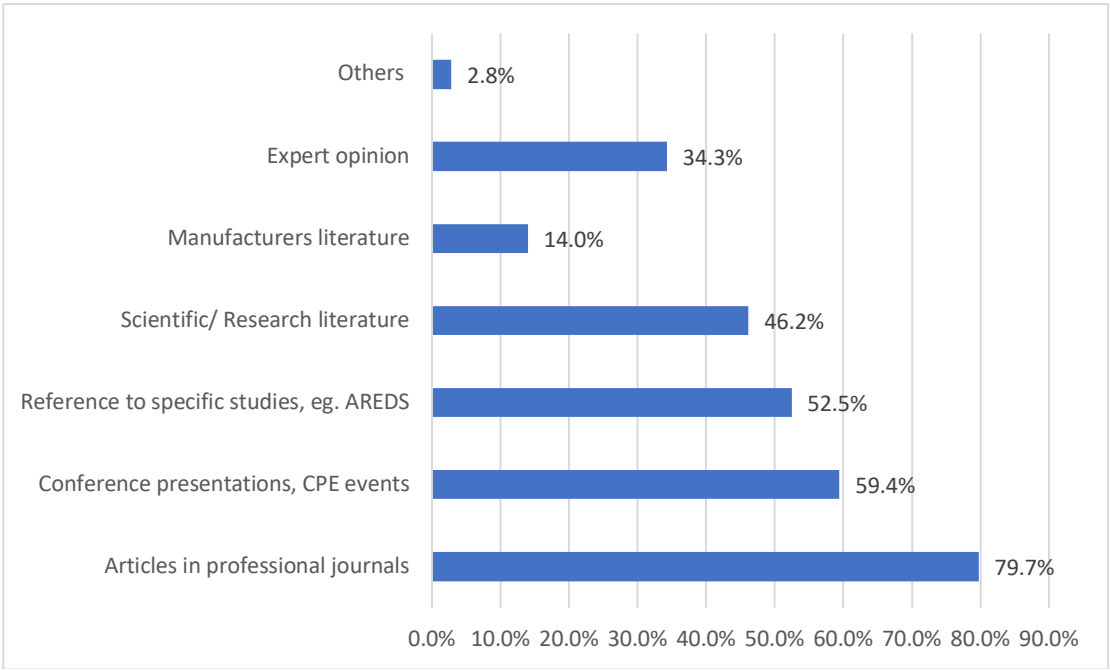

Figure 3.24: Sources of evidence that respondents use to obtain information on nutritional supplements and AMD

Self-efficacy scores

The Mann-Whitney U test is used to analyse the difference in average self-efficacy scores between optometrists with different years of experience, working in different practices and with different qualifications.

Statement	<=12 years of experience	> 12 years of experience	P-Value
1. I am confident that I could classify the type of AMD a patient has based on retinal signs.	68.3 (SD: 11.6)	68.2 (SD: 16.0)	0.98
2. I am confident that I can advise a patient with AMD on the relationship between AMD and nutrition.	69.4 (SD: 10.2)	71.9 (SD: 15.7)	0.63
3. I am confident that I can advise a patient with AMD on what foods to eat that might be beneficial for their condition.	65.3 (SD: 12.6)	65.4 (SD: 15.7)	0.98
4. I am confident that I can advise a patient with AMD on the quantities of food that might be beneficial for their eye health.	54.9 (SD: 12.5)	52.2 (SD: 16.6)	0.63
5. I am confident that I can advise a patient with AMD on when nutritional supplementation may be beneficial.	61.4 (SD: 11.1)	68.8 (SD: 13.9)	0.14
6. I am confident that I can advise a patient with AMD on what supplements to take and what dosage to recommend.	55.1 (SD: 12.5)	58.9 (SD: 16.4)	0.50
7. I am confident with talking about nutrition to those at risk of AMD.	60.6 (SD: 10.8)	63.4 (SD: 20.0)	0.67

Table 3.11: Average confidence and self-efficacy scores between optometrists with less than or 12 years of experience and optometrists with more than 12 years of experience

Out of the seven statements in Table 3.11, there is no item that shows a statistically significant difference in scores between those with or less than twelve years of experience and those with more than twelve years of experience (all p-values are more than 0.05).

Statement	Retail	Clinical	P-Value
1. I am confident that I could classify the type of AMD a patient has based on retinal signs.	60.4 (SD: 23.0)	74.3 (SD: 15.5)	< 0.01
2. I am confident that I can advise a patient with AMD on the relationship between AMD and nutrition.	60.7 (SD: 27.0)	71.5 (SD: 18.5)	< 0.01
3. I am confident that I can advise a patient with AMD on what foods to eat that might be beneficial for their condition.	58.2 (SD: 25.8)	68.0 (SD: 19.2)	0.01
4. I am confident that I can advise a patient with AMD on the quantities of food that might be beneficial for their eye health.	48.6 (SD: 26.4)	53.9 (SD: 23.8)	0.21
5. I am confident that I can advise a patient with AMD on when nutritional supplementation may be beneficial.	56.8 (SD: 25.2)	66.8 (SD: 20.8)	0.01
6. I am confident that I can advise a patient with AMD on what supplements to take and what dosage to recommend.	48.6 (SD: 24.8)	58.0 (SD: 22.3)	0.02
7. I am confident with talking about nutrition to those at risk of AMD.	55.9 (SD: 27.4)	63.9 (SD: 22.2)	0.06

Table 3.12: Average confidence and self-efficacy scores between optometrists working in retail and optometrists working in clinical setting (optical shops, clinics and hospitals)

Between optometrists working in retail and optometrists working in clinical setting, the score difference was statistically significant for all statements except for statements four and seven (p-values > 0.05).

Statement	Diploma	Bachelor, Masters, PhD	P-Value
1. I am confident that I could classify the type of AMD a patient has based on retinal signs.	60.4 (SD: 21.6)	73.1 (SD: 17.4)	< 0.01
2. I am confident that I can advise a patient with AMD on the relationship between AMD and nutrition.	60.8 (SD: 23.3)	71.6 (SD: 21.0)	< 0.01
3. I am confident that I can advise a patient with AMD on what foods to eat that might be beneficial for their condition.	56.7 (SD: 22.6)	68.8 (SD: 20.5)	< 0.01
4. I am confident that I can advise a patient with AMD on the quantities of food that might be beneficial for their eye health.	50.0 (SD: 22.1)	53.0 (SD: 25.7)	0.24
5. I am confident that I can advise a patient with AMD on when nutritional supplementation may be beneficial.	57.5 (SD: 23.8)	66.3 (SD: 21.6)	0.01
6. I am confident that I can advise a patient with AMD on what supplements to take and what dosage to recommend.	48.5 (SD: 25.1)	57.6 (SD: 22.3)	0.01
7. I am confident with talking about nutrition to those at risk of AMD.	53.8 (SD: 25.5)	65 (SD: 22.8)	< 0.01

Table 3.13: Average self-efficacy scores between optometrists with a diploma qualification and optometrists with a bachelor, masters or PhD qualification.

There is a difference in self-efficacy scores for all statements except statement four between optometrists with a diploma qualification and optometrists with a bachelor, masters or PhD qualification.

3.5 Discussion

It is with no doubt that AMD will bring about society impact and economic burden to a country in the years to come due to the ageing population. In Singapore, it has been estimated that there will be a growth of over 42% in the number of wet AMD cases by the year 2030[45]. As AMD affects the patient's central vision, it will have a significant impact on patient's vision and functionality as the condition progresses, therefore compromising patient's quality of life. In view of the society impact and economic burden that AMD will bring in the near future, the Singapore government is taking necessary measures to reduce this impact to a minimum, and one of the measures include the AMD awareness week that is being held annually since 2005. With no treatment available for

atrophic AMD, the modifiable risk factors such as smoking and dietary modification are targeted as they are simple and cost-effective[215], and are being studied extensively to either prevent the development of AMD, or to prevent atrophic AMD from progressing to the more advanced forms such as GA or neovascular AMD.

In Singapore, most optometrists in retail optical shops do not perform a comprehensive eye examination on their patients as most practices are operating alike a traditional optical shop where prescription of glasses is the main focus of business. However, there are some optometrists in retail practice who take reference to the approach optometrists in Western countries are practicing, and being equipped with state-of-the-art equipment so that a comprehensive eye examination can be performed on all patients. This is evident from the results in this study that only 46.4% of the optometrists practicing in retail optical shops routinely perform a fundus examination on patients aged 50 and above, compared with 93.3% of optometrists practicing in clinical optical shops. While more (76.8%) optometrists in retail optical shops routinely perform slit-lamp bio-microscopy on their patients aged 50 and above, but by not routinely performing fundus examination, they could have missed AMD patients especially during the early stages when their vision is usually unaffected.

Though currently there are no large clinical trials to prove that antioxidants or PUFAs are beneficial for early AMD, some optometrists in Singapore (42.6%) do frequently provide dietary advice for patients with early AMD. 81.6% of the optometrists in Singapore advised patients with early AMD to consume green leafy vegetables daily but did not mention the amount to consume, and 60.3% of them advised their patients with early AMD to consume one serving of oily fish daily.

In the UK[209], 3.7% of the respondents never provide dietary advice, 28.4% of the respondents sometimes provide dietary advice, and 67.9% always or most of the time provide dietary advice for patients with established AMD. In another similar study done in Sweden[208], 29% of the optometrists never recommend, 43% sometimes recommend and 28% always or very often recommend on diet for patients with established AMD. In

comparison with our data in Singapore, 9.4% of the clinical optometrists never provide dietary advice, 28.2% sometimes provide dietary advice and 52.9% always or most of the time provide dietary advice for patients with established AMD.

From the study done in the UK[209], 38.3% of the optometrists advised patients with established AMD to eat plenty of leafy green vegetables, 0.2% advised to eat oily fish at least twice per week, 50.7% advised to eat both green leafy vegetables and oily fish and 10.8% advised to eat other foods. 78.0% of the optometrists in this study advised patients with advanced AMD to consume green leafy vegetables, 58.9% advised to consume oily fish and 58.9% advised patients with advanced AMD to consume both green leafy vegetables and oily fish. One of the reasons to explain the higher percentage (58.9%) of Singapore optometrists advising patients with advanced AMD to eat oily fish could be because in this study, the respondents are able to select more than one option; whereas in the study done in the UK, the respondents are only allowed to select one option out of the four options. However, the percentage of optometrists who advised patients with advanced AMD to consume both green leafy vegetables and oily fish is comparable between Singapore (58.9%) and the UK (50.7%).

In the UK,[209] it was found that 53.6% of optometrists always or most of the time provide dietary advice for patients considered to be at risk of AMD, 39.2% sometimes provide dietary advice and 7.2% never provide dietary advice for patients considered to be at risk of AMD. In Sweden[208], 25% of the optometrists always or very often provide recommendations on diet, 42% sometimes provide recommendations on diet and 33% never provide recommendations on diet for patients who are at risk of developing AMD. In Singapore, 31.7% of the clinical optometrists always or most of the time provide dietary advice to patients considered to be at risk of AMD, 45.9% sometimes provide dietary advice and 10.6% never provide dietary advice to patients considered to be at risk of AMD.

In the UK[209] it was established that 38.4% of the optometrists advised patients considered to be at risk of AMD to eat plenty of green leafy vegetables, 0.5% advised to

eat oily fish at least twice per week, 47.2% advised to eat both green leafy vegetables and oily fish and 14.0% advised to eat other foods. In this study, 80.1% of the optometrists advised patients considered to be at risk of AMD to eat green leafy vegetables, 58.9% advised to eat oily fish and 57.4% advised to consume both green leafy vegetables and oily fish.

Lutein and zeaxanthin are the principal components of macular pigment which plays an important role in visual function and also possesses essential antioxidant and protective blue-light filtering properties[216]. These macular carotenoids are not synthesized by the body *de novo* and therefore humans rely solely on dietary intake. The richest sources of lutein and zeaxanthin are from leafy green vegetables such as spinach and kale, and orange or yellow fruits and vegetables. A review by Chong et al. suggested that high antioxidant levels in the healthy retina do little to prevent the development of early AMD[67], while a Cochrane review showed that antioxidant supplements may have a role delaying the progression of early to late AMD[193]. This could explain the varying results relating to dietary advice for patients who are at risk of AMD between optometrists in Singapore, the UK and Sweden.

The frequency of taking a smoking history in new or first time patients amongst optometrists in Singapore was very similar to the study conducted in the UK[209] by Lawrenson and Evans, with one-third of the optometrists in Singapore frequently taking a smoking history, where the proportions of smokers in the UK and Singapore are 19.9%[201] and 28.0%[201] respectively. A survey conducted in 2006 on optometrists and contact lens practitioners practicing in Singapore revealed that 66% were aware that smoking was a risk factor for AMD[212], and through this study, more optometrists (97.87%) in Singapore are now aware that smoking is a risk factor for AMD. Despite being aware that smoking is a risk factor for AMD, only one-third of the optometrists in Singapore would inform AMD patients of the link between smoking and AMD, but almost half will advise AMD patients to quit smoking, with only one-third of the UK optometrists[209] who will do the same. This reveals that Singapore optometrists are more willing to advise

AMD patients to quit smoking as compared to the optometrists in the UK, and it is a good sign since there are more smokers in Singapore than in the UK. There is increasing evidence that smoking is causally linked to the development of AMD[217] and smoking increases the risk of AMD two-fold[218], but public awareness of the link between smoking and ocular health is lacking[219–221]. Therefore, eye care practitioners play a critical role in educating the public the link between smoking and AMD as well as encouraging smokers to quit. Only one-third of the optometrists in Singapore would inform AMD patients of the link between smoking and AMD, but almost half will advise AMD patients to quit smoking if they are current smokers. Previous studies that have investigated the attitudes and practice of optometrists in this area have reported similar findings[222,223]. These studies also identified a number of barriers to routinely addressing a patient's smoking behavior including time constraints and a perceived need for further training in this area[223]. The challenges that Singapore optometrists face when advising AMD patients to quit smoking will be explored in the next chapter, but meanwhile Singapore optometrists should be providing smoking advice to more patients.

With regards to recommending nutritional supplements for AMD patients, similar in the UK, the decision was based on the likelihood of disease progression, with 92.3% of the optometrists in Singapore providing nutritional supplements in scenario with advanced AMD in one eye and early AMD in the other eye. 73.4% of them would recommend an AREDS or AREDS 2 formula, compared to only 26% by optometrists in the UK[209]. However, in the scenario where patient had advanced AMD in both eyes, 88.1% of the optometrists in Singapore would also recommend nutritional supplements, with 71.3% of them recommending the AREDS or AREDS 2 formula. Optometrists in Singapore are likely to recommend nutritional supplements in all three scenarios, but the supplement that they are most likely to recommend in scenario one (55-year old with no evidence of AMD but with one or more parents and/or siblings affected by AMD) are antioxidant vitamins, lutein and zeaxanthin (49%). The nutritional supplements that they will recommend for scenario two and three are based on the latest clinical research evidence,

that is, results from AREDS and/or AREDS 2, and the sources of evidence that they got information on nutritional supplements and the eye are articles in professional journals, conference presentation such as continuing professional education events and references to specific studies such as the AREDS.

At the end of the questionnaire, participants were asked to indicate their self-efficacy score for each statement and comparing the scores between optometrists with less than or twelve years of experience and optometrists with more than twelve years of experience, there is no significant difference in the self-efficacy scores between the two groups of optometrists. This shows that the number of years of experience does not influence the self-efficacy scores among optometrists in Singapore. However, when comparing the average self-efficacy scores between optometrists working in retail practice and optometrists working in clinical setting, there is a statistically significant difference ($p < 0.05$) in the scores between these two groups for all the statements except 1) I am confident that I can advise a patient with AMD on the quantities of food that might be beneficial for their eye health ($p = 0.21$), and 2) I am confident with talking about nutrition to those at risk of AMD ($p = 0.06$). In addition, when comparing the self-efficacy scores between optometrists with diploma qualification and optometrists with higher qualification such as Bachelor, Masters or PhD, optometrists with higher qualification have a statistically significant higher score for all the statements except for one statement: I am confident that I can advise a patient with AMD on the quantities of food that might be beneficial for their eye health ($p = 0.24$). This shows that most optometrists, despite working in a clinical setting or have a higher qualification, are not that confident when asked to advise their AMD patients on the quantities of food that might be beneficial for their eye health.

In conclusion, more optometrists practicing in retail optical shops should routinely perform fundus examination on all patients aged 50 and above so that conditions such as AMD could be diagnosed and treatment or appropriate advice can be provided earlier. Though the percentage of Singapore optometrists providing dietary advice to patients

with advanced AMD is slightly lower as compared to the optometrists in the UK, it is higher than the percentage of Swedish optometrists who will always provide dietary advice to patients with advanced AMD. For patients considered to be at risk of AMD, about one-third of the Singapore optometrists always or most of the time provide dietary advice, similar to the percentage in Sweden. Singapore optometrists are comfortable to provide general nutritional advice to patients with early AMD, hence they do not and are not confident to provide the quantities of food to consume for such patients. In addition, Singapore optometrists felt that they lack knowledge in this area, therefore patients with advanced AMD should be managed by an ophthalmologist.

More optometrists in Singapore are willing to advise AMD patients to quit smoking than the optometrists in the UK, even though only one-third of the Singapore optometrists explain to AMD patients the link between smoking and AMD. Most optometrists in Singapore will recommend nutritional supplements based on disease progression and their recommendations are based on latest clinical research; AREDS and AREDS 2 findings. Years of experience practicing as an optometrist does not affect the confidence and self-efficacy scores but the type of practice as well as level of qualification does affect the confidence and self-efficacy scores for most of the statements.

The prevalence of AMD in Singapore has been predicted to increase over the next few years and with the relatively high prevalence of smokers, the frequency of nutritional and smoking advice to AMD patients by optometrists should be higher. In the next chapter, Singapore optometrists' opinions on nutrition and the eye will be explored through face-to-face in-depth interviews. In addition, the challenges faced and support required by optometrists when providing nutritional and smoking advice to AMD patients will be discovered in the next chapter. This will complement and provide a clearer picture on the statistics presented in this chapter.

Chapter Four: What do Singapore optometrists feel about providing nutritional and smoking advice to patients with or at risk of AMD?

In the previous chapter, the frequency of nutritional and smoking advice to patients with or at risk of AMD provided by optometrists in Singapore was evaluated and compared with results published from the UK and Sweden. In addition, the confidence level of Singapore optometrists when providing nutritional and smoking advice to patients with or at risk of AMD was assessed using self-efficacy scores. In this chapter, a qualitative research of how Singapore optometrists feel about providing nutritional and smoking advice to patients with or at risk of AMD will be conducted via in-depth interviews.

4.1 Introduction

As discussed in earlier chapters, cigarette smoking, diet and nutritional supplementation are major modifiable factors that have a strong influence on the long-term risk of neovascular AMD. This is align with the hypothesis that oxidative stress plays an important role in the pathogenesis of AMD. Thus a diet rich in certain vitamins (A, C and E), nutrients such as xanthophyll carotenoids (lutein and zeaxanthin) and omega-3 essential fatty acids could help to delay a patient with atrophic AMD to neovascular AMD, as some of these substances have been shown to scavenge ROIs that were produced through oxidative stress. The studies that evaluated the association between nutrition and AMD were discussed earlier in Chapter 2.3. Cigarette smoking is generally quite well known to the public to be associated with systemic morbidities such as lung cancer, cardiovascular disease and stroke, and associations with eye diseases such as AMD are less widely recognized[224]. In order to increase public awareness on the association between cigarette smoking and eye diseases, one of the measures was to include eye images as graphic warnings on cigarette packaging. Cigarette smoking is also known to increase oxidative stress, which can result in an increased risk of AMD, and the details on the association between smoking and AMD were highlighted previously in Chapter 2.4.

As the major providers of primary eye care, optometrists are ideally positioned, as part of the health care team, to provide patient counselling with regard to these modifiable risk factors for AMD. In addition, optometrists could be the first to diagnose AMD in some patients through a comprehensive eye examination and could therefore give a timely diagnosis and management. In recognition of the important public health role that optometrists provide in these areas, there has been interest in understanding current optometric practices in these domains, as shown by studies done in the UK[209], United States[225] and Canada[223].

However, there is limited or no qualitative research conducted to explore optometrists' views regarding nutrition and the eye in Singapore, or even other countries. Dietary advice and nutritional advice or management are often used interchangeably. According to McClinchy et al.[226], dietary advice relates to the nutritional care or management of a specific disorder such as type 2 diabetes, undernutrition, obesity. Those providing dietary advice will need to have some specific knowledge about diet and disease. This is oppose to general nutritional advice given as part of life-style related care or health education included within a health promotion intervention. In the case of AMD, patients can be provided with dietary or nutritional advice depending on the severity of the condition. During category 1 or 2 AMD, patients can be advised on general nutritional advice such as to increase their intake of lutein and zeaxanthin with green leafy vegetables, and/or omega 3 with oily fish such as salmon. However for category 3 or 4 AMD, the AREDS and AREDS 2 results show that nutritional supplements containing vitamins A, C, E, carotenoids such as lutein and zeaxanthin and minerals such as zinc and cooper could prevent the condition from worsening and become neovascular AMD. In this case, providing dietary advice will be applicable. "Dieticians are the only qualified health care professionals that assess, diagnose and treat dietary and nutritional problems.{Citation}" McClinchy et al.[227] found that general practitioners (GPs) and practice nurses perceived that their role included the delivery of dietary advice and Mitchell et al.[228] confirm that primary care is an appropriate setting for GPs and practice nurses to deliver dietary

advice. Therefore, optometrists are in an ideal position to provide either nutritional or dietary advice to AMD patients as they provide primary eye care but no research has been done on optometrists to evaluate on how they perceive their role to provide nutritional and dietary advice.

The previous chapter has looked into the nutritional and smoking advice that optometrists in Singapore are providing, and it was found that the frequency of Singapore optometrists providing nutritional and smoking advice to patients with or at risk of AMD is not as high as anticipated. The prevalence of AMD in Singapore has been predicted to increase due to the ageing population and with the higher prevalence of smokers compared with other Western countries, it is important to understand Singapore optometrists' views about nutrition and the eye, particularly AMD. Following the results of the previous study, Singapore optometrists' perspectives as well as challenges when providing nutritional and smoking advice to AMD patients will be further explored in this chapter. These will be addressed through a qualitative research presented in this chapter, whereby there will be a better understanding on the optometrists' views regarding nutrition and the eye, their perception on this role, the challenges that they face, as well as further support in this domain.

4.2 Methods

Study design

The main objective of this study is to obtain an in-depth opinion from Singapore optometrists on nutrition and the eye through interviews and to further enhance some findings that was observed from the previous chapter, such as a lower than anticipated frequency of nutritional and smoking advice to patients with or at risk of AMD.

Qualitative research methods are employed when the researcher is interested in understanding the "why" behind peoples' behaviours and actions. It provides a way to get an in-depth understanding of the underlying reasons, attitudes, and motivations behind various human behaviours[229]. Observations, in-depth interviews and focus

groups are methodologies in qualitative research that may be used to collect data[230]. In-depth interviews involve the posing of open-ended questions and follow-up probes designed to obtain an in-depth understanding of participants' experiences, perceptions, opinions, feelings and knowledge[231]. Interviews are useful for gaining insight and context into a topic, in this case, nutrition and the eye, and there is opportunity to probe, to encourage more complete and better explained responses. There is total control over the environment; the interviewer can ensure that the interview in conducted in private such that no other person may constitute bias to the response of the interviewee, and the interviewer can also ensure that sufficient information is being collected through the interview process[232]. Focus groups are structurally similar to in-depth interviews in the sense that they are comprised of open-ended questions designed to capture the in-depth experiences of respondents[233]. However, focus groups are a distinct data collection technique from in-depth interviews, which will provide researchers with data that relies upon the interaction of the group members to formulate answers to the researcher's questions[230]. One-to-one in-depth interviews are preferred over focus groups in this study phase as the main objective is to obtain optometrists' individual views; focus groups might result in an imbalance of opinions between optometrists and optometrists who are more vocal will share more of their views, whereas optometrists who are more reserved might not voice out their views as much. Moreover, any doubts during the interview can be clarified immediately and hence interviews are the best option for this phase of the study. It was also highlighted by Rosenthal[230] that it is not recommended that novice researchers undertake focus groups in a first attempt to conduct qualitative research.

In the previous study discussed in chapter three, the questions were mostly closed-ended with the intention to increase the response rate as well as to enable easier data analysis. However, this could also create some questions regarding nutrition and the eye to be unanswered but able to be complemented through this study. The questions were developed by the principal researcher and were created to answer queries that emerged

while analysing the data from the previous study. Some of the queries include how do optometrists feel about providing nutritional and smoking advice to their patients, and how receptive were their patients when they provide such advice, the challenges that they face when providing nutritional and smoking advice and the support that they hope to get in this area. There were no previous research conducted in this area on optometrists, but a similar study by McClinchy et al[226] exploring the views of pharmacists and allied health professionals regarding the provision of dietary advice to patients was used as a reference while developing the questions.

The questions of the semi-structured interview are:

- Do you think nutrition plays a role in preventing or treating certain eye conditions? What are the eye conditions that you think will benefit from nutrition? (*For each eye condition, what nutritional advice/information have you given to patients? Or for each eye condition, what kind of nutritional advice/information do you think is appropriate for patients?*) Where do you get the information regarding nutrition and the eye from?
- What were your patients' reactions to you offering this advice/information? (*If participants have not engaged in this scenario, ask whether participants believe that patients would expect optometrists to be involved in this type of activity and why?)*
- How do you feel about including nutritional advice/information within your patient management?
- What factors influence whether or not you give nutritional advice/information to your patients? What do you think is most challenging/difficult when providing nutritional/ smoking advice to AMD patients?
- Do you routinely screen for age-related macular degeneration (AMD) in your practice for patients aged 50 years and above? (*If yes, ask how is AMD diagnosed in your practice? If no, ask what is/are the main reasons for not routinely screening?)* Currently the use of diagnostic drugs has not been legalized in Singapore, but do you think the use of these drugs will aid in your diagnosis of AMD?

- If you agree that you have an important role to play in the health promotion and dietary advice giving to patients, what can be done to support you further in your professional development relating to this aspect of your role?
- Are there any other comments you would like to make in relation to this area of patient care and management?

Sample size and data collection

Optometrists in Singapore typically can work in different settings: 1) retail optical shop, 2) clinical optical shop, 3) teaching institution or 4) eye clinic or eye hospital. As highlighted in chapter three and to re-emphasize, 1) optometrists working in retail optical shops mainly only check subjective refraction and anterior ocular health as patients usually go to them for vision correction, such as to purchase glasses or contact lenses. Therefore optometrists working in retail optical shops generally do not routinely perform comprehensive eye examinations on all patients. 2) Optometrists working in clinical optical shops will perform a comprehensive eye examination on all patients even though the location and setting is similar to that of a retail optical shop. The scope of practice is adopted from western countries whereby a comprehensive eye examination is performed on all patients. 3) Optometrists working in teaching institutions are lecturers who are teaching Optometry in an educational institution such as a polytechnic, and are also practising Optometry in the clinic that is usually located within the school compound. 4) Optometrists working in hospitals and eye clinics will perform optometric tests as requested by the ophthalmologists. Data from OOB show that 60% of fully registered optometrists work in retail setting (retail optical shops and clinical optical shops) and the rest are working in eye clinics or hospitals.

Optometrists from different settings are recruited for this research to ensure a varied opinion from optometrists working in Singapore and the optometrists are recruited from the contact list of the principal researcher. A total of fifteen fully registered optometrists are recruited for this research; 3 are from retail optical shop, 4 are from clinical optical

shops, 5 are from teaching institutions and 3 are from eye clinics or eye hospitals. Data collection and analysis were conducted concurrently and participant recruitment ceased when data saturation has appeared to have surfaced. Saturation is used in qualitative research as a criterion for discontinuing data collection and/or data analysis[234]. Its origin lie in grounded theory[235] but it now commands acceptance across a range of approaches to qualitative research, and Guest et al.[236] refer saturation as having become 'the gold standard by which purposive sample sizes are determined in health science research."

A face-to-face interview was arranged with the participants based on their schedules and all interviews were conducted by the principal researcher. Prior to each interview, the study information (Appendix H) was discussed with the participant, and the consent form (Appendix I) signed, should the participant have no further questions on the research. The participants are provided with the questions at least a day before the interview so that they could have time to think about their answers. They are also informed that the interviews will be voice-recorded for data analysis.

Inclusion criteria

• Fully registered optometrist under the Optometrists and Opticians Board (OOB) in Singapore

• Currently practicing in Singapore as an optometrist, either working in a retail optical shop, clinical optical shop, hospital, eye clinic or teaching institution.

Exclusion criteria

• Optometrists under provisional registration

• Optometrists currently not practicing in Singapore

Ethical approval

This study has been reviewed and approved by the Parkway Independent Ethics Committee (PIEC) reference number PIEC/2017/004 (Appendix E) based in Singapore

and the Aston University Research Ethics Committee (AUREC) application number 2010 based in the UK.

Data-analysis

Material collected through qualitative methods is invariably unstructured and unwieldy; a huge proportion of it is text based, consisting of verbatim transcriptions of interviews or discussions, field notes or other findings that were documented during data collection. Moreover, the internal content of the material is usually in detailed and micro form, such as accounts of experiences, descriptions of interchanges, or observations of interactions. The qualitative researcher has to provide some coherence and structure to this cumbersome data set while retaining a hold of the original accounts and observations from which is it derived. Qualitative data analysis is essentially about detection, and the tasks of defining, categorizing, theorizing, explaining, exploring and mapping are fundamental to the analyst's role[237]. The methods used for qualitative analysis therefore need to facilitate such detection, and to be of a form which allow certain functions to be performed. 'Framework analysis' is one of the methods deployed for qualitative analysis and is an analytical process which involves a number of distinct though highly interconnected stages: familiarization, identifying a thematic framework, indexing, charting, mapping and interpretation. In this study, 'framework analysis' as described by Ritchie and Spencer[238] is used for data analysis and unlike quantitative analysis, qualitative analysis occurs concurrently with data collection. In addition, this process is conducted manually, without the assistance of any software as the amount of data is still manageable. The process of data analysis begins during the data collection; with the principal researcher skilfully facilitating the discussion, generating rich data from the interviews which have been recorded individually, and typing the transcript following each interview with the optometrists. This stage is followed by familiarization with the data which is achieved by listening to the recorded interviews, reading the transcripts

several times in order to immerse in the details and get a sense of the interview as a whole before breaking it into parts.

The next stage involves identifying a thematic framework by writing memos in the margin of the text in the transcripts in the form of short phrases, ideas or concepts arising from the texts and beginning to develop categories. This stage is also facilitated as the interview questions were semi-structured. After manually sorting out the ideas and short phrases, the themes or descriptive statements that arise are: 1) Singapore optometrists' perception of nutrition and the eye; 2) Perception of optometrists providing nutritional advice – optometrists' and patients' view; 3) Factors and challenges faced by Singapore optometrists when providing nutritional advice in practice; 4) Further support required by Singapore optometrists in the area of nutrition and the eye. The third stage, indexing, comprises sifting the data, highlighting and sorting out quotes and making comparisons both within and between cases. Each individual transcript was printed on paper and analysed thoroughly, and quotes were highlighted with different colours based on the optometrist's practice type. The fourth stage, charting, involves lifting the quotes from their original context and re-arranging them under the newly-developed appropriate themes. The quotes that were highlighted earlier were then cut out and placed into the respective themes as mentioned earlier. The data are then ready for the final stage of analysis, that is, mapping and interpreting; to make sense of the individual quotes, to see the relationship between the quotes, and the links between the data as a whole. With the quotes highlighted in different colours, it was easier to compare data between optometrists from various practice types. As mentioned in the previous section, data collection ceased when the same comments were heard several times during the interviews, indicating that saturation has occurred. Similarly, saturation has occurred when no new codes were generated from the data collected. Themes that were decided upon while analysing the transcripts will be discussed further in the next results section.

4.3 Results

Fifteen fully registered optometrists were interviewed for this research; 3 are from retail optical shop, 4 are from clinical optical shops, 5 are from teaching institutions and 3 are from eye clinics or eye hospitals. Of these fifteen optometrists, fourteen of them obtained a Bachelor of Optometry and one had a Diploma in Optometry.

4.3.1 Singapore optometrists' perception of nutrition and the eye

All the optometrists who were interviewed agree that nutrition plays a role in preventing and managing, rather than treating certain eye conditions, and the condition that all mentioned will benefit from nutrition would be age-related macular degeneration (AMD). This is largely due to the Age-Related Eye Disease Study (AREDS)[4] that was conducted and proved that vitamins such as A, C, E, cooper and zinc minerals and beta-carotene are beneficial in slowing the progression of moderate AMD to advanced AMD. In addition, AREDS 2[64] found that antioxidants such as lutein and zeaxanthin are also beneficial for AMD patients. Other sources that the optometrists obtained information regarding nutrition and the eye include continuing professional education (CPE) programs, conferences, online websites such as WebMD or supplement suppliers' website, journal articles as well as brochures from eye hospitals or clinics.

"*For AMD, I do read through the AREDS, which is 1 and 2."* (retail optometrist 3)

"*Through articles, reading journals online, conferences."* (institution optometrist 2)

The nutritional advice optometrists provide to AMD patients range from having a balanced diet, to consuming foods that are high in antioxidants such as green leafy vegetables, kale, spinach, broccoli, eggs, carrots, wolfberries and different kinds of coloured fruits, to supplements that either contain the AREDS formulation, lutein or antioxidants. Most optometrists do not mention the specific supplement except for two optometrists (institution optometrist 4 and clinical optometrist 2) who will recommend

Preservision, two (retail optometrist 2 and institution optometrist 5) who would recommend Ocuvite and one optometrist (clinical optical shop optometrist 2) who would recommend Lutex 15. One optometrist (clinical optometrist 3) will offer Macutec in the eye clinic where she is working in. Optometrists recommended Preservision as it contains ingredients from AREDS 1 and 2 study; Lutex 15 was recommended by the optometrist in this study as clinical trials were done to prove its efficacy. However, it was not further explored with optometrists the reasons for recommending Ocuvite. In terms of dietary advice, all the optometrists did not advise on the frequency and quantity to be consumed, and all optometrists, except for two optometrists, will advise their patients to get their supplements outside of their practices, such as the local chemists. Hence they do not and are unable to advise patients on the frequency as well as dosage for these supplements.

"*I didn't tell them about the frequency, I didn't tell them how often they should take or how much they should take."* (retail optometrist 1)
"*No, I don't. I think as long as a decent amount of egg every day I think is fine."* (institution optometrist 4)
"*So for AMD we are prescribing this lutein supplement known as Lutex 15."* (clinical optical shop optometrist 2)

One optometrist (clinical optical shop optometrist 1) mentioned that she will advise all her patients aged 50 and above to have a balanced diet and to include more green leafy vegetables in their diet. Some optometrists will advise their patients with early AMD on dietary modifications, and supplements for patients with moderate AMD, while one optometrist will advise supplements for mild to moderate AMD. With more advanced AMD, patients are usually seen by the ophthalmologists and optometrists would usually advise such patients to seek the ophthalmologists' opinions on supplements.

"*Usually from diet first, you do not necessarily have to go for supplements straight away, you may go for the antioxidant diet first, then of course lifestyle change, like stop smoking, if patients are smoking. If they have been diagnosed of dry AMD by the ophthalmologists and they would like to know what they can do, then we will further advise supplements."* (retail optometrist 2)

"*I will prescribe when the AMD condition is mild to moderate, but if it is advanced or severe, I will refer to the ophthalmologist and they will recommend the supplements accordingly."* (clinical optical shop optometrist 2)

"*So I will normally ask them to check with their ophthalmologists, as AMD patients would normally be already seen by ophthalmologists. There could be a reason why the doctor said yes or no to supplements."* (clinical optical shop optometrist 1)

Following AMD, the next common eye condition that optometrists in Singapore will provide nutritional advice is dry eyes. However, as the evidence suggesting that nutrition is beneficial for dry eyes is not strong or controversial, most of the optometrists will only provide such advice when patients ask.

"For dry eye, some studies say omega-3 or omega-3 & 6 may improve the symptoms, but more recent one suggest not so useful. I do not usually advise on this area" (clinical optometrist 1)

"If patients have signs or symptoms of dry eyes, usually the first line of management would be ocular lubricants, and if it is a long-standing case of dry eyes, then we can include supplements such as omega-3 fatty acids on top of the ocular lubricants." (institution optometrist 4)

The nutritional advice that they will provide for dry eye patients would be to increase their intake of omega 3 or 6 fatty acids or to get supplements containing omega 3 or 6. Similar to AMD, most optometrists do not advise dry eye patients on the frequency and quantity

to be consumed. One optometrist (clinical optical shop optometrist 2) will only prescribe omega-3 supplements for dry eyes if it is either the inflammatory or aqueous-deficient types, and another (clinical optometrist 3) recommends Lacritec to her dry eye patients.

"I do not have a fixed regime that I will recommend nutritional supplements for every dry eye patient. Maybe me myself is not so convinced, but if patients ask me what to take for dry eyes then I will mention things like omega 3, omega 6. I do not know of any particular brand." (clinical optical shop optometrist 3)

The other eye conditions that optometrists provide nutritional advice are refractive errors such as myopia, diabetic retinopathy, hypertensive retinopathy and cataract. One optometrist would recommend carrots or vitamin A for refractive errors (institution optometrist 5) while the another (institution optometrist 3) mentioned that if his patient's parents ask if there is any particular food that could help in myopia, he would advise a well-balanced diet, for instance if the child is lacking vitamin A in his daily diet, it would be good to increase his intake of foods that are high in vitamin A. Diabetic retinopathy and hypertensive retinopathy occur due to systemic conditions such as diabetes, high blood pressure or high cholesterol. Therefore if patient controls these systemic conditions by controlling their diet or taking supplements, it will also help to control these eye conditions. Last but not least , one optometrist (retail optometrist 1) would recommend his patients with cataract to increase their intake of antioxidants, if his patients ask him for recommendations.

4.3.2 Perception of optometrists providing nutritional advice – optometrists' and patients' view

All optometrists felt positive about providing nutritional advice to their patients, and most felt that it should be a part of routine management for patients with moderate AMD, as currently there is no known treatment for atrophic AMD. Therefore, most optometrists felt

that as long as it is proven to be beneficial, AMD patients have the right to know what is good for their condition, including from a nutrition point of view.

"*I think it is good, I suppose this is the least that we can do, at least you do have some form of management for the patient, rather than just send them away."* (clinical optical shop optometrist 1)

"As a practitioner I feel that any advice that can help patient to prevent or slow down or treat their eye condition or even actually being able to help them in their lifestyle, it will be a good piece of advice to all patients. I am happy to provide the information to the patient." (retail optometrist 3)

To some optometrists, providing nutritional advice can actually help to differentiate themselves from other optometrists who are not, as it will give patients an impression that they are providing them with a holistic care, rather than just checking their prescription and prescribing them with glasses or contact lenses, alike what the opticians or some optometrists are currently doing.

"*Definitely it does help because it will increase the professionalism of optometrists, and also because not all shops do this as well. Having a step forward shows that you are more concerned about your patient's eye health so it will really stand out more compared to others."* (clinical optical shop optometrist 3)

"*Yes, definitely, I suppose it will build the trust between you and the patient, and the patient will look at you from a different perspective, one who is more clinical and shows more concern with regards to their eye health, rather than one who only does refraction and dispensing of glasses."* (clinical optical shop optometrist 1)

Despite feeling positive about providing nutritional advice, there were also some concerns and restrictions for some optometrists. The key challenges will be discussed in more details in the next section.

"*To me, if you just want to provide advice and then for them (patients) to decide whether they want to purchase it from outside, that I am comfortable. But if you are asking me to prescribe or sell it, then I might not be as comfortable in that sense."* (institution optometrist 1)

"*I feel that it can benefit patients and I should definitely do that. Although I do need some brushing up on advice to be given."* (clinical optometrist 2)

The optometrists feel that from patients' point of view, they are generally quite receptive about optometrists providing them with nutritional advice, but there are also some who are surprised that optometrists are giving them nutritional advice as to them, as to these patients, these advices are usually provided by either doctors or pharmacists. Conversely, there are also few patients who are not convinced and feel that optometrists are trying to sell another product to them. In a general nutshell, patients have to be educated on what the condition is, how it came about, and with concrete evidence, they will then be advised on why nutrition will work for them. Some optometrists will provide nutritional advice as an option for the patient to explore on their own, rather than to prescribe to their patients.

"*I think they are usually positive because many people have been giving nutritional advice, including the pharmacists, it is quite common to give nutritional advice. I think optometrists giving nutritional advice is alright, I think people are quite receptive to it."* (institution optometrist 4)

"*50% of patients who were offered supplements were agreeable with trying them out but the other half of them were questioning the benefit of supplements."* (clinical optometrist 3)

4.3.3 Factors and challenges faced by Singapore optometrists when providing nutritional advice in practice

The main factors that determine whether to provide nutritional advice or information to patients will depend on the condition that patient is having, the stage and/or risk factors of the condition, as well as patient receptiveness. Some optometrists will be more cautious when providing nutritional advice to patients with chronic systemic conditions and on medications, and will advise such patients to consult their doctors to evaluate if they are suitable to take any form of supplements. Two optometrists from retail consider chair time as one of the factors as in a busy practice, optometrists might not be able to provide too much nutritional information to their patients when there are other patients waiting to be seen. On the other hand, there are also optometrists (from institution) who will routinely provide nutritional advice to all their AMD patients.

"*It will depend on the diagnosis of the disease, and also during which stage of the disease that I will put my emphasis on all these nutritional advice to the patient. Some of the factors that may affect is it may take up more chair time in the practice, and also response from the patients."* (retail optometrist 3)

"*Whether to elaborate or not I guess will depend on whether the patient is open to it. If I sense a bit of resistance, it will be more like a statement rather than asking them to consider buying this or that. The first attempt is like planting the idea, and if they are very open then we may discuss more."* (clinical optical shop optometrist 2)

"*Generally there is no factor, I think it is like a routine that I will let them know that this option is available."* (institution optometrist 1)

The key challenge that most optometrists face when providing nutritional advice to AMD patients would be their lack of knowledge in this area, such as the type of nutritional advice (dietary modification or supplements) for different stages, including the type of food, the amount, as well as the frequency. Some optometrists are also concerned if the nutritional supplements that they are going to recommend will cause any adverse effect(s) to the body if the patient is taking other medications. One of the optometrist (clinical optical shop optometrist 3) mentioned that the challenge is actually to get patients to have a comprehensive eye examination, as the Singapore population is still not used to the concept of having a comprehensive eye examination in an optical shop setting; they would usually do it in eye clinics or eye hospitals. Therefore without conducting a comprehensive eye examination, it would be impossible to diagnose AMD, moreover to provide nutritional advice. Another optometrist further added that patients usually visit them for vision correction, therefore if they provide such advice, the patients might doubt their competency and their role. Chair-time and patient compliance are also some of the challenges that the optometrists face when providing nutritional advice to AMD patients.

"I think telling them is not challenging, the challenging part is whether they take it in or not." (retail optometrist 2)

"*The challenge is, patients see us as vision providers, and they will seek ophthalmologists for their AMD condition. They will not see us as being proficient in AMD.*" (retail optometrist 1)

"If the patient is rejecting the idea of having a full comprehensive eye exam, which comprises of the front and back eye health, but some patients only want a degree check, so it will be difficult for us to even move on to the nutritional part if they do not want to have a front and back health assessment done." (clinical optical shop optometrist 3)

"*Most challenging or difficult would be to give them specific examples on how much dietary supplements is ideal or sufficient. We are aware that anti-oxidants, green vegetables, eggs, fruits and etc are beneficial for AMD, but how much exactly is required.*

So I don't usually go into those details as I am not really sure myself. I would just tell them (patients) to include those food into their meals." (clinical optical shop optometrist 1)

"Sometimes I find that I don't think I have enough knowledge, I myself may not be competent enough, because ultimately as we mentioned earlier, our exposure to this is also quite new, if we have more knowledge, more people giving us the kind of information, I think we will be more confident in giving out advice. Also the mindset, because in Singapore when patients come to us they are looking for visual correction, refractive error correction, I mean if we give them the advice on supplements or even medicine advice, they may question on our competency and our role, as in are we stepping into the role of a medical practitioner or pharmacists." (clinical optical shop optometrist 4)

"First will be the specific food to consume, eg. If I mention green leafy vegetables, which type should patients consume? And also in terms of frequency and quantity, it is very difficult for me to answer. And also sometimes when I mention to consume more carrots, and they will ask me, what about if I drink carrot juice, is it the same? It is very hard for me to answer yes or no, because yes, sometimes it is fiber, but we know that some of the nutrients could be lost if we blend the food and make it into a juice." (institution optometrist 3)

"Chair-time. Therefore sometimes it would be helpful if there are pamphlets or brochures that can do the explanation." (institution optometrist 1)

There were some controversy between optometrists on smoking advice to AMD patients. All optometrists agree that smoking is linked to AMD but for some optometrists they will only inform their AMD patients on the risk of progressing to advanced AMD if they are smokers. They will not reinforce the need to quit smoking as they feel that most of the smokers would have been smoking for a long period of time, and getting them to quit would be difficult and challenging, especially when there are no visual symptoms during the early AMD stages. On the other hand, there are optometrists who will routinely advise

AMD patients to quit smoking, but usually by first asking their patients to taper their smoking frequency. And for these optometrists, patients' compliance would be a challenge as they usually do not follow up with these patients. One optometrist working in clinical optical shop had no issues advising his patients to quit smoking as he feels that this is due to his age, and culturally it is acceptable, as compared to a junior optometrist in his or her twenties advising his or her patient who is much older to quit smoking.

"*Usually I will not advise AMD patients to quit smoking directly. Because usually for AMD patients they could have been smoking for an extended period of time, so it is just letting them know that smoking is one of the trigger factors, but I will not put it down as advice to stop smoking.*" (institution optometrist 1)

"*I will give, but I will not put it as strongly as nutritional advice, although I know that smoking contributes a huge factor in terms of AMD. As I believe most smokers would have been advised before me, so why would they listen to me and not to others who would have advised them long time ago."* (institution optometrist 3)

"*Yes I do, usually during history taking we will indicate whether the patient is a smoker, and if they do, I will ask how long can one pack of cigarettes last. Most patients who have drusen-like changes in their retina, I will advise them to slowly cut down, as it is difficult for them to put a total stop to it. By tapering down can actually help them, as long as they are convinced, I am sure they are able to cut down their smoking habits."* (clinical optical shop optometrist 3)

"No, I don't think it is a big challenge, because maybe I am old, so if I give advice sometimes people will listen, but if the junior optometrist was to tell a senior person not to smoke, so sometimes culturally may not be so, it may be a little bit of challenge, it you have a twenty-plus optometrist telling an older man not to smoke, sometimes there may be a hurdle." (clinical optical shop optometrist 4)

4.3.4 Further support required by Singapore optometrists in the area of nutrition and the eye

All the optometrists have an unanimous conclusion that they have an important role to play in providing nutritional advice to their patients, particularly AMD patients and there are several ways that can be done to support them further in this area. First and foremost, most of the optometrists think that they need to be equipped with deeper knowledge and skills in this area; they would like to have more updated evidence-based information so that they can be more confident when communicating such advice, which in turn will allow their patients to have more confident in them. Also, optometrists should also upgrade their skills to diagnose AMD, in which they would be able to manage their patients accordingly and appropriately. Secondly, with so many supplements that are currently in the market that are marketed to be beneficial for the eye, optometrists would like to have a review on all the available products from a neutral party, as well as a guideline on the types of nutritional advice for AMD patients at different stages as well as the "contraindications" for those with systemic conditions or are taking any form of medications. Additionally, educational materials for patients, in the form of brochure, pamphlets or even website that caters to the Singapore community would help to save some chair time. One optometrist (clinical optical shop optometrist 2) mentioned that there should be regular exchange of updates on how ophthalmologists or general practitioners (GPs) care for their patients, so that optometrists know whether they are co-managing their patients correctly, and also whether their advice is in tune with the rest of the health care professionals. Last but not least, the public needs to have more awareness and confidence of the capabilities of the optometrists in Singapore that they do have the skills and knowledge to diagnose eye conditions and provide management that includes nutritional advice.

"*If the professional or government bodies come up with a set of practice guidelines, we can refer them to advise our patients accordingly."* (clinical optometrist 1)

"I suppose public awareness of the optometrists, that we are trained and skilled in detecting eye diseases and providing advice to patients, and nowadays I think there are more public awareness campaigns going on, like TV shows, news coverage on optometrists and what they could do. So I think this is something that has been on-going and I think this is good, we just have to educate the public that there is this profession that could give advice, and we do know about all these diseases." (clinical optical shop optometrist 1)

"*The general public does not view us as primary eye care provider and therefore less willing to pay for our services. Furthermore, based on our demographics, it is not difficult to have access to ophthalmologists who can provide them with diagnosis and treatment together. The reason why patients allow us to monitor is because of cost (cheaper as compared to ophthalmologist)."* (retail optometrist 1)

"I think the Health Promotion Board should also bring out some public awareness on what is AMD and what are the foods that they can consume so that the public can have a rough idea of if the supplement does help or not, because it is really by authority promoting the health, so this will improve the trust on supplementations." (clinical optical shop optometrist 3)

"I think in terms of information we have to constantly keep updated, because things may change, I think most of the time the challenge to me is quantity and any interactions with anything else." (clinical optical shop optometrist 2)

"Maybe have refresher courses for optoms and public education to convince patients that our advice can be trusted!" (clinical optometrist 2)

"*I think pharmaceutical companies are not reaching out to the optometrists to provide them with the brochures, and to let them sell the supplements. If pharmaceutical companies can recognize the optometrists are doing a lot to detect AMD, and doing a lot of screening for AMD, then pharmaceutical companies will approach optical establishments to let them sell their nutritional products."* (institution optometrist 4)

"I believe there are a few ways. 1) There could be more education in this part, so that everyone in Singapore would have a general guideline to say to patients in terms of different stages of AMD. 2) If there are certain websites or brochures or pamphlets that dedicate to this portion, and preferably be in multi-languages and that will help in Singapore context as most of the people above 50 sometimes are unable to speak English." (institution optometrist 3)

4.4 Discussion

Nutritional supplements are becoming more common among consumers as not only can they supplement the nutrients that people are lacking in our diet, they are also useful for certain ailments and patients are seeking for a 'natural' remedy rather than to depend on medication. The sale of vitamins and supplements in Singapore was SGD490 million in 2017, up by nearly SGD40 million in 2012[239]. According to the newspaper report, the increase in sales was contributed by busy young adults, parents and the elderly. Busy young adults typically buy vitamins and dietary supplements to obtain the necessary nutrients as they are usually too busy to eat proper meals, parents tend to buy probiotics as well as brain and immunity-boosting supplements for their children and seniors buy glucosamine for joints or eyecare products. From this study, the two most common eye conditions that optometrists provide nutritional advice are AMD and dry eyes. This is similar to the study conducted by Downie[210] whereby 91.2% and 63.9% of the Australian optometrists recommend nutritional supplements to patients with AMD and dry eyes respectively.

Despite strongly believing that nutrition plays a part in eye health, Singapore optometrists feel that they are lacking knowledge in this area and therefore are unable to provide adequate nutritional advice to their patients. This include the specific type of food or foods to consume, the amount as well as the frequency. In addition, the type of food that is available in Singapore could be different from Western countries. In Singapore, when Chinese patients are asked to consume green leafy vegetables, the type of vegetables

that Chinese usually consume are different from the kale or spinach that Caucasians consume in Western countries. Hence the nutritional value may no longer be the same and may not serve the same purpose. AMD patients are usually the elderly and they could also suffer from other chronic systemic conditions or are taking other medications, therefore optometrists feel that it will be better if they could have more knowledge on the type of medical conditions or medication that can be affected by nutritional supplements. This additional knowledge on nutrition and the eye could be provided to the optometrists through training, continuing education programs or a website that all optometrists could have access to. All the optometrists who participated in this study are aware of the link between smoking and AMD but not all will actively advise AMD patients to stop smoking as they feel that it is a relatively difficult habit to kick and patients might not be compliant. On the other hand, based on the previous study, only 20% of Singapore optometrists always take a smoking history in follow-up patients, hence there is also a low chance for Singapore optometrists to follow-up on patients who were compliant and really did quit smoking.

The optometrists in this study were recruited from different practice settings to compare if optometrists working in different setting will have a different perspective on nutrition and the eye. However from this study, the views on the themes did not differ much between optometrists from the four practice settings. The only difference highlighted would be for optometrists working in retail setting, chair time is one of the determining factors whether they will provide nutritional advice to their patients. If there are patients waiting to be seen, optometrists in retail optical shops might not provide nutritional advice to their patients. Singapore optometrists are willing to be trained and enhance their knowledge in this domain but at the same time they will be even more confident if there is a guideline for them. In situations whereby chair time is limited, brochures or pamphlets for patients will come in handy. Nonetheless, the public needs to be more aware of the competency of the optometrists in Singapore, to know that they are capable of

diagnosing and managing certain eye conditions, and not only checking their refractive status and offering visual corrections.

From the previous study (chapter three), it was learnt that Singapore optometrists are not providing dietary and smoking advice to AMD patients as frequently as they should. Through this study, it was found that Singapore optometrists believe that nutrition does play a part in promoting eye health but most felt that they lack the knowledge to provide such information to their patients. Through the in-depth interviews, some optometrists would like to have a guideline that could assist them when providing nutritional advice to AMD patients. Therefore in the next study, that will be discussed in the coming chapter, the efficacy of a clinical decision-making aid will be evaluated on whether it can assist optometrists when providing nutritional advice to AMD patients.

Chapter Five: Evaluation of a clinical decision-making aid for qualified and student optometrists when providing nutritional advice for patients with or at risk of age-related macular degeneration

In the previous chapter, Singapore optometrists' views on nutrition and the eye was explored through in-depth interviews. In this chapter, the efficacy of a clinical decision-making aid (CDMA) for qualified and student optometrists when providing nutritional advice for patients with or at risk of AMD will be evaluated.

5.1 Introduction

As AMD has been found to be highly linked to oxidative stress, there has been much interest among researchers in the use of antioxidant supplementation for reducing the risk of progression. The first large clinical trial was the Age-Related Eye Disease Study (AREDS)[4] conducted in 2001 and since then, carotenoids such as lutein and zeaxanthin have been identified as nutrients that can provide a protective role against progression of AMD due to their antioxidant and photo-protective properties[240], but these nutrients are only made available through diet and the levels could be affected by the digestive and absorptive systems[240]. More recently, the Age-Related Eye Disease Study 2 (AREDS 2) found that AMD patients who took a supplement containing lutein and zeaxanthin had their risk of progression reduced by 18%[64].

Despite results from both AREDS and AREDS 2, there remains confusion among AMD patients and eye care practitioners about when and what supplements should be taken and the type of foods to be consumed[83]. Following the results of AREDS 2, the Macular Society, a UK charity, have advocated the use of AREDS 2 formulation, where appropriate, and eating vegetables that are lutein and zeaxanthin rich; such as eggs, spinach and kale[241], but recent surveys of its members found that many were not taking a clinically proven nutritional supplement[84] or consuming adequate amounts of lutein and zeaxanthin[242]. In Singapore, unlike medicines, health supplements are currently not subject to approval, licensing or registration before they can be sold locally. Additionally,

they are not assessed for their effectiveness by the Health Sciences Authority (HSA), unlike medicines which are studied for their efficacy based on data from stringent clinical trials before they are granted approval to be administered to patients. Therefore there are at least twenty different types of nutritional supplements for the eye in a local chemist and aggressive marketing of particular nutritional formulations makes it difficult for, especially AMD patients, and eye care practitioners to make research-based choices, and research has shown that given more choices, patients can become overwhelmed[83]. Online platforms are another source where patients can obtain information but some unreliable sources might provide conflicting information as to which are the best dietary sources of lutein and zeaxanthin. Other barriers that prevent patients from taking preventive measures for AMD progression include poor communication with eye care practitioners, misinformation in the marketplace, and age-related compliance problems[83]. Patients reported that eye care practitioners were not giving consistent advice regarding nutrition and reported confusion as to what advice, if any, to follow[213]. However, there are currently no guidelines for eye care practitioners to follow when advising patients about nutrition, and from the qualitative study presented in the previous chapter, eye care practitioners would like to have a guide in this area. Eye care practitioners are often unsure, or lack confidence, when giving advice outside of their area of expertise, even when this advice is consistent with general health advice[243]. A study conducted by Downie at al[244]. shows that Australia optometrists need to enhance their knowledge on nutritional supplementation in managing their own health, particularly improving their understanding of what a healthy diet is and its role in eye health.

5.2 Methods

This is an interventional study to evaluate whether a clinical decision-making aid (CDMA) (Figure 5.1) in the form of a flowchart will boost an optometrist's (qualified or student) confidence and self-efficacy when providing nutritional advice to patients with or at risk of AMD.

Design of the clinical decision-making aid

When eye care practitioners provide clinical care to patients, they are required to rapidly analyse information acquired during the eye examination. This process of clinical reasoning is inherently linked to decision making, being a fundamental aspect of care delivery. Decision making can range from fast, intuitive or heuristic decisions through to well-reasoned, analytical, evidence-based decisions that drive patient care[245]. There is a spectrum of decision making – at one end of the spectrum eye care practitioners use their intuition and experience to decide clinical care for patients with simple, common conditions. At the other end of the spectrum where complex decisions with a high level of uncertainty need to be made, eye care practitioners will adopt a more methodical approach in order to feel supported, and these include clinical guidelines, rules-based heuristics, evidence-based principles or even previous experience gained in 'similar' situations[245]. When making clinical decisions, particularly under time constraints, eye care practitioners often rely on "heuristics", cognitive shortcuts that reduce cognitive burden by focusing on certain pieces of information rather than considering the full range of available information[246]. Although heuristics may lead to accurate decisions, they can also be associated with systematic cognitive errors, known as "cognitive biases", which can result in incomplete or inaccurate reasoning. Eye care practitioners are susceptible to a range of cognitive biases, which can result in misdiagnoses, delayed clinical care, and/or patient mismanagement.

Similar to other healthcare practices, an evidence-based approach is considered the essential foundation for making clinical decisions in eye care practice. Evidence-based medicine/practice can be defined as integrating the judicious use of current best evidence in clinical decision making, together with patient values and clinical expertise[247]. When managing an individual patient, a series of steps can be applied to formulate a strategy for him. These steps include articulating a clinical question, gathering evidence to answer the questions, evaluating the quality and validity of the evidence, and finally deciding how to apply the evidence to the care of a given patient[248]. However this type

of decision making mitigates the use of unnecessary resources and can be time consuming. Therefore it is often reserved for only the very complex clinical cases[248] as the pressures of current health systems continue to increase.

Clinical decision making models have been described in medicine for many years, particularly for front-line doctors and nursing staff. Researchers in the field of nursing Banning et al.[249] proposed that there are three main types of clinical decision making models: information processing, intuitive-humanist and O'Neills multidimensional model. The information processing model uses a scientific or hypothetical-deductive approach to assist metacognitive reasoning that is essential to medical diagnosis[250,251]. In this model, decision trees are used to numerically assess potential outcomes; for each decision tree, possible outcomes are assigned a numerical value and the probability of attaining an outcome is assessed. In the intuitive-humanist model, practitioners use their experience and intuition to make clinical decisions instead of relying on guidelines or scientific reasoning. The O'Neills multidimensional model is a theoretical model based on a computerised decision support system that uses both hypothetico-deduction and pattern recognition as a basis for decision making[249]. This key elements of this model include pre-encounter data, anticipating and controlling risk, the provision of standard nursing care, client and situational modifications, and finally hypothesis generation and action. This model takes into consideration the many variables that could exist in life which makes a guideline inappropriate, and inexperienced practitioners can easily input the data to generate an answer.

Organizations such as the National Institute for Health and Care Excellence (NICE) and World Health Organization (WHO) have created clinical guidelines according to evidence based principles and the consensus of a panel of experts. Patients are often put into a category or group, and the guideline will follow a 'if, then' rule with a number of multi-steps for questions that are particularly complex[248]. These guidelines are often inflexible and at times can be difficult to place some patients into specific categories, but can be invaluable for a busy overstretched clinical practice. Sometimes these clinical guidelines

are depicted using decision-making aids such as decision trees, flow charts, and brainstorm and mind map diagrams.

In medicine, flowcharts have been used to aid diagnosis, treatment options and advice given to patients[252]. As symbols or diagrams are used in flowcharts, users can process information quickly and therefore are ideal in settings where time is limited. In addition, flowcharts are often space efficient and can be placed on clinic walls or work desk such that practitioners can have easy access. As such, a flowchart makes an ideal CDMA for all eye care practitioners to use and an ideal way to implement an intervention for consistent nutritional advice for patients with or at risk of AMD. A flowchart was designed by researchers at Aston University, School of Health Sciences[213] to take eye care practitioners through a decision-making process that would determine whether a patient matched the AREDS 2 eligibility criteria for supplementation. The flowchart helps eye care practitioners to answer the following question: 'what nutritional advice should be given to patients with, or at risk AMD?' The most recent large-scale clinical research available to answer this question is the AREDS 2[64]; the study's inclusion and exclusion criteria can be used to decide when it is appropriate to advise the AREDS 2 nutritional formulation.

The flowchart was designed in the following manner: the top of the flowchart begins with consideration of the retinal examination. If a patient has normal macula, but with a family history of AMD, a branch of decisions will help to determine whether they would benefit from dietary modification. If a patient does not have a normal macula, the branches following will determine whether the patient fitted into the AREDS 2 inclusion criteria or whether they would benefit from dietary modification only. If the retinal findings were not related to AMD, referral for an ophthalmological opinion was advised. The final outcomes were split into either dietary modification (advice one) or supplementation (advice two).

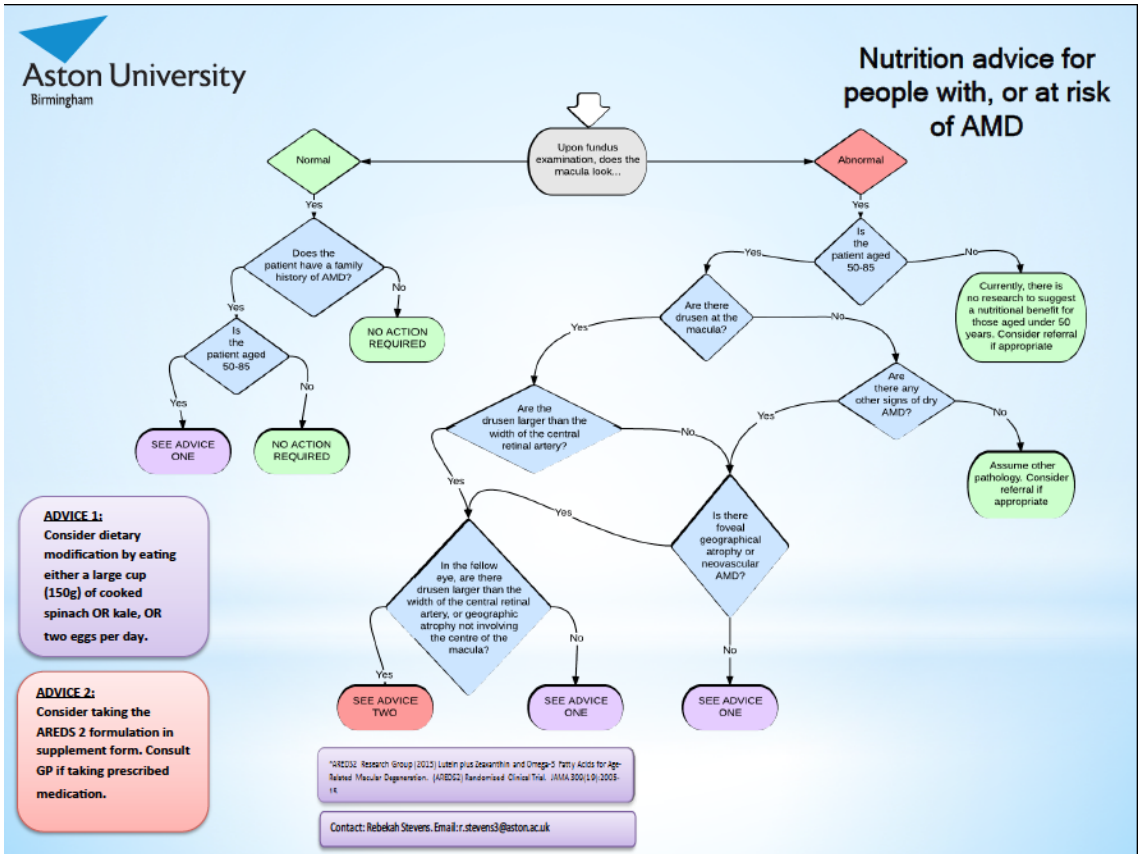

Figure 5.1: Clinical decision-making aid in the form of flowchart[213] to assist eye care practitioners when providing nutritional advice to patients with, or at risk of AMD

Evaluation of the flowchart

A key outcome of using the flowchart is to increase the confidence of eye care practitioners when providing dietary advice to AMD patients and this can be achieved using self-efficacy surveys. Self-efficacy refers to a person's estimate of his or her ability to perform a specific task successfully[253], including a measure of the confidence that a person has in their ability to perform a behaviour, such as to give dietary advice to AMD patients[254]. In this study, self-efficacy is measured to assess if the flowchart could boost an eye care practitioner's confidence, and evaluating self-efficacy using scales give researchers an idea of whether a subject is likely to accomplish a task in the future. Organisational research has shown that self-efficacy is a valuable way of evaluating healthcare practitioners' behaviours as it can predict the performance of an individual[255]. Self-efficacy scales have been used in many surveys when evaluating healthcare practitioners' confidence in performing certain procedures or giving advice to

patients[243,254,256]. Moreover, a survey of clinicians perceptions of computerised protocols demonstrated that the biggest predictor of intention to use a computerised protocol was beliefs about self-efficacy[64], highlighting how important self-efficacy is in providing advice for practitioners.

As mentioned, self-efficacy is concerned with perceived capability, therefore efficacy items should accurately reflect the construct[257]. As described by Bandura that in the standard methodology for measuring self-efficacy beliefs, "individuals are presented with items portraying different levels of task demands, and they rate the strength of their belief in their ability to execute the activities" [257]. A survey was created that asked participants to rate their confidence and self-efficacy out of 100 (in 10 increment steps) when performing certain tasks such as giving nutritional advice to patients or classifying the type of AMD seen in a patient. As people usually avoid the extreme positions, so a scale with only a few steps may in actual use shrink to one or two points[257]. In addition, too few steps in a scale loses differentiating information as people responding to a category may differ if intermediate steps were included. Hence an efficacy scale with the 0 to 100 response format is a stronger predictor of performance than one with a 5-interval scale[258]. The items in this survey was taken with reference to the study done by Stevens et al.[213], and further details of the study will be discussed in the next section. These items were chosen because they cover all decisions that need to be contemplated when determining when and what nutritional advice should be given to a patient based on the AREDS 2 criteria[213], that is, determining that a patient had drusen and geographic atrophy, advising a patient that AMD and nutrition are linked, determining what foods are beneficial and how much, knowing which patients require supplementation, which supplements to take (and how much) and advising those who have a family history of AMD or are at risk. Demographic information such as age, gender, and the number of years practising (where appropriate) were also obtained. A self-efficacy was repeated by participants after using the flowchart. This survey was the same as the initial survey before using the

flowchart and utilized the same items to rate the participant's confidence and self-efficacy from 0 to 100 in 10 increment steps.

A. I am confident that I could classify the type of AMD a patient has based on retinal signs
B. I am confident that I can advise a patient with AMD on the relationship between AMD and nutrition
C. I am confident that I can advise a patient with AMD on what foods to eat that might be beneficial for their condition
D. I am confident that I can advise a patient with AMD on the quantities of foods that might be beneficial for their eye health
E. I am confident that I can advise a patient with AMD on when nutritional supplementation may be beneficial
F. I am confident that I can advise a patient with AMD on what supplements to take and what dosage to recommend
G. I am confident with talking about nutrition to those at risk of AMD

Table 5.1: Seven-item survey to assess confidence and self-efficacy

Hypothetical case scenarios or vignettes

Hypothetical case scenarios or vignettes partially describes real-life situations and are used in research and education as a strategy to elicit participants' attitudes, judgements, beliefs, knowledge, opinions or decisions[259]. Hypothetical case scenarios or vignettes offer a relatively low cost and flexible strategy for describing and understanding hypothetical decision-making in any national or international context, regardless of whether they may or may not reflect actual decision-making[259]. Vignettes can be incorporated with a wide range of behavioural, psycho-social, clinical, environmental or health system factors[259]; and when it is not possible to include all relevant combinations of factors in the vignettes, the use of unbiased methods for choosing what factors to include will be needed. The use of clinical case scenarios or vignettes is central to problem-based learning in healthcare education and common in practice guideline and decision support studies[260].

There are two main methods of scenario or vignette development that can be distinguished in the field of healthcare and social sciences: the factorial and the storytelling method[259]. The factorial method involves creation of vignettes based on a set of predefined factors that describe all or a subset of possible combinations seen in a situation or decision problem. As more levels and factors are considered, the number of combinations of factor categories increases very rapidly, making this method challenging to be applied practically. In contrast, the storytelling method involves creation of one or more 'typical' or 'illustrative' scenarios by members of the research team, often based on their experience. The five clinical case scenarios utilised in this study was created with the storytelling method.

Previous use and validation of flowchart/ CDMA

The objective of the flowchart was to create a clinical decision making aid that increases practitioner knowledge on nutrition and AMD, as well as less inter-practitioner variability when giving nutritional advice to AMD patients. This CDMA was created by Stevens et al.[213] and modified following a pilot with 25 optometrists. Thereafter, the CDMA was tested and validated on qualified and student optometrists from the UK, with the results published in 2017.

In the study, 46 qualified optometrists completed the self-efficacy surveys before and after using the CDMA and 51 student optometrists were also recruited for this study. Out of the 51 student optometrists, 25 of them were given an article on AREDS, while 26 were given the CDMA as the intervention of the study. Qualified optometrists showed a significant increase in confidence scores from the initial survey (M=69.7%, SD=16.2%) to the second survey after use of the CDMA for 2 weeks in their practices (M=82.1%, SD=11.6%; $t(45) = 7.33$, $p<.001$). The student optometrists also increased confidence scores after receiving the CDMA (M of first survey = 41.7%, SD = 14.6%; M of second survey = 69.1%, SD = 1.7%; $t(25) = 7.92$, $p<.001$), and increased the number of correct answers on five clinical scenarios.

Ethical approval

This study has been reviewed and approved by the Parkway Independent Ethics Committee (PIEC) reference number PIEC/2017/004 (Appendix E) based in Singapore and the Aston University Research Ethics Committee (AUREC) application number 2010 based in the UK.

Recruitment and delivery protocol

This study is sub-divided into two parts as it was conducted on two different groups of participants: qualified optometrists and student optometrists.

Qualified optometrist recruitment. Optometrists who participated in the first study "Nutritional and smoking advice to patients with or at risk of AMD by optometrists in Singapore" as presented in chapter three were asked to indicate if they are interested to participate in this study. Participants who were interested left their contact details such as email address or contact number. Using the GPower software, the sample size required for this group of qualified optometrists is 27, based on the effect size from the study done by Stevens[213]. This sample size was also confirmed by manually calculating using a mathematical formula. In order to compare if years of experience would affect the results, the target sample size is 27 for experienced optometrists (with more than twelve years of experience) and 27 for non-experienced optometrists (less than or equal to twelve years of experience)

Delivery protocol. Participants who indicated their interest to participate in this study were contacted for a meeting with the principal researcher of this study. Before commencing the study, contents of the study information sheet (Appendix J) was discussed and consent form (Appendix K) was signed. Five hypothetical clinical scenarios of patients in different AMD stages (Figure 5.2) was presented to the participant. For each case scenario, retinal photographs were provided, together with information about the patient's age, the type of AMD they had, and if there was any family history of AMD

underneath the photographs. Each case was designed to simulate possible scenarios that practitioners could encounter in real practices, and also taking into consideration recommendations from AREDS 1 and 2 that only category 3 or 4 AMD patients will benefit from supplements. The clinical scenarios were also cross-referenced to the study by Stevens et al.[213], and three out of five scenarios (case number 1, 2 and 4) were similar. After looking through each case scenario, the participant was asked to indicate their nutritional advice for each scenario from a list of ten options:

1) Consider lifestyle changes to reduce risk, e.g. not smoking, wearing sun protection etc.

2) Consider increasing your intake of lutein. For example, you could try to eat either a large cup (150g) of **cooked** spinach OR kale, OR two eggs every day

3) Consider increasing your intake of lutein. For example, you could try to eat either a large cup (150g) of **uncooked** spinach OR kale, OR two eggs every day

4) Consider increasing your intake of lutein. For example, you could try to eat either a small cup (75g) of cooked spinach OR kale every day

5) Consider dietary modification by eating 2 bananas or 2 mangos every day

6) Consider taking supplementation of vitamin C 500mg, vitamin E 400IU, lutein 10mg, xeaxanthin 2mg, zinc 25mg, copper 2mg every day. Consult GP if taking prescribed medication.

7) Consider taking the vitamin C 250mg, vitamin E 800IU, lutein 1mg, xeaxanthin 5mg, zinc 250mg, copper 20mg every day. Consult GP if taking prescribed medication.

8) Consider taking supplementation of lutein 10mg and xeaxanthin 2mg every day.

9) Consider taking supplementation of gingko biloba and cod liver oil every day.

10) Refer immediately for wet AMD treatment.

The participant was then briefed on the usage of the CDMA by the principal researcher and to indicate their nutritional advice for the five clinical scenarios again, but with the

assistance of the CDMA. As mentioned previously, participants also completed the self-efficacy survey before and after using the CDMA.

Student optometrist recruitment. Final year optometry students studying at Ngee Ann Polytechnic pursuing their Diploma in Optometry were invited to take part by the principal researcher who is working there as the clinical supervisor, in the knowledge that their participation was voluntary and that they were not obliged to take part. Using the GPower software and based on the study done by Stevens[213] to obtain the same effect size, the sample size required for this group of student optometrists is 8. This sample size was also confirmed by manually calculating using a mathematical formula. In order to assess the difference between the CDMA and standard clinical materials such as an article on AREDS, there will be two groups of student optometrists.

Delivery protocol. Student optometrists were arranged to meet with the principal researcher based on the students' schedule. The study information sheet (Appendix L) and consent form (Appendix L) were given to the students prior to the meeting and the consent form has to be signed by the parent or guardian of the student, as the students are below the age of 21. The students were randomly assigned to either the CDMA group or the 'article' group, and the protocol was the same as the qualified optometrists, except for the 'article' group whereby the students were given an article to read instead of the CDMA.

Figure 5.2(a): Five hypothetical clinical scenarios of patients in different AMD stages

Figure 5.2(b): Five hypothetical clinical scenarios of patients in different AMD stages

5.3 Results

Participants

A total of 50 qualified optometrists participated in this study; 23 males and 27 females with a mean age of 36.3 ± 9.4 years old. The average number of years practicing as a fully registered optometrist for these participants is 13.4 ± 8.8 years. The Kolmogorov-Smirnov one-sample test showed that the data of the qualified optometrists did not exhibit a normal distribution (p=0.047), therefore the non-parametric Wilcoxon signed-rank test was used for data analysis.

A total of 15 student optometrists participated in this study; consisting of 7 males and 8 females with a mean age of 19.1 ± 0.7 years old. Of the 15 student optometrists, 7 were allocated to the CDMA group and 8 were allocated to the AREDS 2 article group. The Kolmogorov-Smirnov one-sample test showed that the data of the student optometrists exhibited a normal distribution (p=0.200). However, due to the low sample size, the paired t-test and Wilcoxon signed-rank test will be run and compared for this group of participants.

Qualified optometrists study: results

Reliability of the scale items in the surveys was confirmed using Cronbach's alpha coefficient (a measure of internal consistency, i.e., how closely related a set of items are as a group). Alpha values were high on each occasion = 0.957 for the first survey, alpha =0.97 for the second survey. Test-retest correlations between scores at both time points confirmed the reliability of the scale ($r = 0.8$, $p<0.01$)

For average confidence scores, there were no differences found between gender or the number of years practising as an optometrist. Hence, these variables did not appear to influence confidence levels.

	<= 12 years of experience	> 12 years of experience
Number of participants	21	29
First survey mean confidence score (0-100)	62.5 ± 9.5	62.9 ± 16.0
Second survey mean confidence score (0-100)	76.0 ± 9.6	76.6 ± 9.5

Table 5.2: Average confidence scores between number of years practicing as an optometrist. ($p > 0.05$ for both surveys)

	Males	Females
Number of participants	23	27
First survey mean confidence score (0-100)	62.8 ± 16.1	63.1 ± 21.6
Second survey mean confidence score (0-100)	75.5 ± 14.0	78.5 ± 15.8

Table 5.3: Average confidence scores between males and females. ($p > 0.05$ for both surveys)

Table below depicts the percentage confidence scores for each statement in the self-efficacy survey, before (first survey) and after (second survey) using the CDMA. A Wilcoxon signed-rank test showed there was a significant increase in mean confidence scores after the participants used the CDMA for the five clinical scenarios, as compared to before (Mean confidence score before = 62.9, SD = 19.1; Mean confidence score after = 77.1, SD = 15; $p < 0.01$).

Confidence Statement	**First Survey (n = 50)**	**Second Survey (n = 50)**	**p-value**
A: I am confident that I could classify the type of AMD a patient has based on retinal signs.	70.6 (SD=18.3)	74.8 (SD=16.7)	0.012
B: I am confident that I can advise a patient with AMD on the relationship between AMD and nutrition.	67.8 (SD=21.8)	77.2 (SD=15.7)	<0.01
C: I am confident that I can advise a patient with AMD on what foods to eat that might be beneficial for their condition.	67.8 (SD=21.3)	78.8 (SD=15.6)	<0.01
D: I am confident that I can advise a patient with AMD on the quantities of food that might be beneficial for their eye health.	55.0 (SD=21.8)	77.8 (SD=16.4)	<0.01
E: I am confident that I can advise a patient with AMD on when nutritional supplementation may be beneficial.	62.8 (SD=22.4)	77.8 (SD=16.7)	<0.01
F: I am confident that I can advise a patient with AMD on what supplements to take and what dosage to recommend.	53.8 (SD=24.2)	76.8 (SD=16.5)	<0.01
G: I am confident with talking about nutrition to those at risk of AMD.	62.8 (SD=22.5)	76.6 (SD=17.1)	<0.01
Mean confidence score	62.9 (SD=19.1)	77.1 (SD=15.0)	<0.01

Table 5.4: Mean confidence scores for each statement between first and second survey among qualified optometrists

Scenario questions

Tables 5.5-5.7 depict the answers given to the five clinical scenarios in the initial survey and then in the second survey after using the CDMA. For statistical analysis, a correct answer was given a value of '1' and incorrect answers were given a value of '0'. The final value was the sum of the answers, out of a possible 5. An independent t-test shows that the number of correct answers significantly increased ($p < 0.001$) after using the CDMA.

Answer option	Scenario One (Correct answer F)	Scenario Two (Correct answer B)	Scenario Three (Correct answer A)	Scenario Four (Correct answer j)	Scenario Five (Correct answer B)
A	4%	48%	4%	0%	2%
B	8%	8%	12%	0%	16%
C	0%	10%	10%	0%	4%
D	2%	12%	2%	0%	2%
E	0%	2%	0%	0%	0%
F	42%	6%	44%	6%	50%
G	4%	2%	14%	0%	14%
H	2%	10%	6%	0%	6%
I	0%	2%	2%	0%	0%
J	38%	0%	6%	94%	6%

Table 5.5: Answers given to five clinical scenarios without the assistance of the CDMA. Shaded cells are the correct answers.

Answer option	Scenario One (Correct answer F)	Scenario Two (Correct answer B)	Scenario Three (Correct answer A)	Scenario Four (Correct answer j)	Scenario Five (Correct answer B)
A	0%	2%	50%	2%	4%
B	12%	92%	16%	24%	74%
C	2%	4%	2%	0%	2%
D	0%	0%	0%	0%	0%
E	0%	0%	0%	0%	0%
F	80%	2%	14%	0%	18%
G	2%	0%	0%	2%	0%
H	0%	0%	2%	0%	0%
I	0%	0%	2%	0%	0%
J	4%	0%	14%	72%	2%

Table 5.6: Answers given to five clinical scenarios with the assistance of the CDMA. Shaded cells are the correct answers.

Scenario	Correct answer percentage (Before)	Correct answer percentage (After)
One	42%	80%
Two	8%	92%
Three	4%	50%
Four	94%	72%
Five	16%	74%

Table 5.7: Percentage of correct answers for case scenarios before and after using CDMA.

Student optometrists study: results

Reliability of the scale items in the surveys was confirmed using Cronbach's alpha coefficient; alpha values were high on each occasion = 0.877 for the first survey, alpha =0.952 for the second survey. Test-retest correlations between scores at both time points confirmed the reliability of the scale ($r = 0.51$, $p = 0.05$).

Group	Survey 1 mean confidence score	Survey 2 mean confidence score
Article	45.2 ± 16.2	57.7 ± 18.7
CDMA	32.2 ± 14.3	70.4 ± 14.6

Table 5.8: Mean confidence score between groups 'Article' and CDMA and between survey 1 and 2

Paired t-tests showed that there is a significant increase in the mean confidence score after using the CDMA and article: Group 'Article' ($p = 0.005$), group CDMA ($p < 0.001$). The Wilcoxon signed-ranked test showed the same results: p-value for group CDMA is 0.018 and the p-value for group 'article' is 0.017. There was not a statistically significant difference in second survey's confidence scores between the two groups, although group CDMA scores are higher than group 'Article'.

Confidence Statement	First survey Group 'Article'	Second survey Group 'Article'	First survey Group CDMA	Second survey Group CDMA
A	61.3 (SD=17.3)	68.8 (SD=18.9)	44.3 (SD=25.1)	74.3 (SD=9.8)
B	52.5 (SD=12.8)	58.8 (SD=16.4)	47.1 (SD=16.0)	68.6 (SD=13.5)
C	45.0 (SD=25.1)	57.5 (SD=16.7)	38.6 (SD=23.4)	74.3 (SD=18.1)
D	32.5 (SD=19.1)	52.5 (SD=21.9)	22.9 (SD=17.0)	70.0 (SD=22.4)
E	38.8 (SD=25.9)	56.3 (SD=25.0)	34.3 (SD=22.3)	67.1 (SD=20.6)
F	41.3 (SD=21.0)	51.3 (SD=24.7)	12.9 (SD=11.1)	64.3 (SD=22.3)
G	45.0 (SD=22.0)	58.8 (SD=18.1)	25.7 (SD=23.7)	74.3 (SD=16.2)

Table 5.9: Mean confidence levels (0 – 100) for the seven statements

Scenario questions

Tables 5.10-5.15 depict the answers given to the five clinical scenarios in the initial survey and then in the second survey according to each group. For statistical analysis, a correct answer was given a value of '1' and incorrect answers were given a value of '0'. The final value was the sum of the answers, out of a possible 5. An independent t-test showed that the number of correct answers increase significantly ($p < 0.05$) after using the CDMA, but not for the group 'Article'. An independent t-test also showed that there was a significant difference between the two group's answers in the second survey – Group CDMA answered significantly more correctly then group 'Article' $t(6) = 2.59$, $p = 0.03$.

Answer option	Scenario One (Correct answer F)	Scenario Two (Correct answer B)	Scenario Three (Correct answer A)	Scenario Four (Correct answer j)	Scenario Five (Correct answer B)
A	1 (14.3%)	5 (71.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)	2 (28.6%)
C	0 (0.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	1 (14.3%)
D	0 (0.0%)	1 (14.3%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
E	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
F	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	2 (28.6%)
G	1 (14.3%)	1 (14.3%)	0 (0.0%)	1 (14.3%)	1 (14.3%)
H	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)
I	1 (14.3%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)
J	3 (42.9%)	0 (0.0%)	0 (0.0%)	4 (57.1%)	0 (0.0%)

Table 5.10: Answers given to five clinical scenarios without the assistance of the CDMA. Shaded cells are the correct answers.

Answer option	Scenario One (Correct answer F)	Scenario Two (Correct answer B)	Scenario Three (Correct answer A)	Scenario Four (Correct answer j)	Scenario Five (Correct answer B)
A	0 (0.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)
B	4 (57.1%)	5 (71.4%)	0 (0.0%)	2 (28.6%)	3 (42.9%)
C	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
D	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
E	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)
F	3 (42.9%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	4 (57.1%)
G	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)
H	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
I	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
J	0 (0.0%)	0 (0.0%)	1 (14.3%)	5 (71.4%)	0 (0.0%)

Table 5.11: Answers given to five clinical scenarios with the assistance of the CDMA. Shaded cells are the correct answers.

Scenario	Correct answer percentage (Before)	Correct answer percentage (After)
One	0.0%	42.9%
Two	0.0%	71.4%
Three	0.0%	28.6%
Four	57.1%	71.4%
Five	28.6%	42.9%

Table 5.12: Percentage of correct answers for case scenarios before and after using CDMA.

Answer option	Scenario One (Correct answer F)	Scenario Two (Correct answer B)	Scenario Three (Correct answer A)	Scenario Four (Correct answer j)	Scenario Five (Correct answer B)
A	1 (12.5%)	4 (50.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)
B	2 (25.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)
C	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)
D	0 (0.0%)	0 (0.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)
E	0 (0.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
F	4 (50.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	4 (50.0%)
G	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
H	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
I	1 (12.5%)	3 (37.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
J	0 (0.0%)	0 (0.0%)	2 (25.0%)	7 (87.5%)	0 (0.0%)

Table 5.13: Answers given to five clinical scenarios before reading the AREDS article. Shaded cells are the correct answers.

Answer option	Scenario One (Correct answer F)	Scenario Two (Correct answer B)	Scenario Three (Correct answer A)	Scenario Four (Correct answer j)	Scenario Five (Correct answer B)
A	1 (12.5%)	5 (62.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)
C	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
D	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)
E	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
F	4 (50.0%)	1 (12.5%)	2 (25.0%)	0 (0.0%)	3 (37.5%)
G	1 (12.5%)	0 (0.0%)	2 (25.0%)	0 (0.0%)	3 (37.5%)
H	1 (12.5%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)
I	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
J	1 (12.5%)	0 (0.0%)	0 (0.0%)	8 (100%)	0 (0.0%)

Table 5.14: Answers given to five clinical scenarios after reading the AREDS article. Shaded cells are the correct answers.

Scenario	Correct answer percentage (Before)	Correct answer percentage (After)
One	50.0%	50.0%
Two	0.0%	0.0%
Three	12.5%	0.0%
Four	87.5%	100%
Five	0.0%	0.0%

Table 5.15: Percentage of correct answers for case scenarios before and after reading the AREDS article.

5.4 Discussion

Within the qualified optometrists, the mean confidence scores increased significantly for each statement after using the CDMA. An interesting finding was discovered from the results. Even though the CDMA did not assist the participants to classify the type of AMD a patient has based on retinal signs, there was a statistically significant increase in mean confidence score for that statement. This shows that with the aid of a guideline, the confidence level of a practitioner generally improves. The number of correct answers for the five clinical scenarios also increased significantly after using the CDMA, except for case number 4, where the patient presented with neovascular AMD in one eye. Some optometrists were too focused on utilizing the CDMA and neglected the fact that the patient should be referred immediately for treatment. Hence, it should be emphasized that the CDMA serves only as a guide for atrophic AMD and optometrists are advised to use their clinical judgement when managing their patients. Overall, the CDMA is useful in boosting the optometrists' confidence when providing nutritional advice to patients with or at risk of AMD and it also help optometrists to provide the appropriate nutritional advice. The results would be even more convincing if the optometrists were to use it in their practices, but because the number of AMD patients seen by Singapore optometrists is quite low, hence this study is designed using clinical scenarios instead.

Within the student optometrists, the mean confidence scores increased significantly for each statement for both groups. However, the number of correct answers for the clinical scenarios increased significantly only for the group CDMA. In addition, the number of correct answers increased for all five scenarios after using the CDMA, but for group

'article', the number of correct answers reduced for scenario three, and there was no difference in the number of correct answers for scenarios one, two and five. The confidence level increased among the student optometrists after using some form of aid (CDMA or article), but the appropriate advice was only provided by the group CDMA. This shows that the CDMA is beneficial for both qualified and student optometrists when providing nutritional advice to patients with or at risk of AMD.

The study done by Stevens et al. [213] evaluated the efficacy of the same CDMA with the same self-efficacy survey that were utilized in this study and the results also show that the CDMA does increase the confidence of both qualified and student optometrists in the UK when providing nutritional advice to patients with or at risk of AMD. The qualified optometrists in the UK completed the self-efficacy survey after using the CDMA in a real practice setting, whereas the qualified optometrists in Singapore completed the self-efficacy survey based on simulated clinical case scenarios. The clinical case scenarios in this study were created using the storytelling method and while efforts were made to simulate real-life situations as closely as possible and to test all the possible clinical scenarios, there still remain some areas of improvement. A modified factorial method could be adopted; the factors to consider can include patient's smoking history, presence of any chronic systemic conditions, visual acuity, and other relevant test results such as Amsler or OCT. With these additional information, the optometrist would be able to provide a more holistic management for the patient. Testing the efficacy of the CDMA in a real practice setting would be ideal, but for some practices, optometrists might not be seeing AMD patients as frequent as other optometrists, and therefore would not be able to give an accurate feedback on the CDMA. Nonetheless, the studies conducted in the UK and Singapore show that the CDMA does improve the confidence of qualified and student optometrists when providing nutritional advice to patients with or at risk of AMD, proving that this CDMA is beneficial for optometrists around the world, regardless of geographic location.

There were other studies in the field of healthcare that have shown that clinical guidelines improved the self-efficacy of healthcare professionals. In the study by Farrell et al.[261], the implementation of evidence-based deprescribing guidelines increase clinicians' self-efficacy in developing and implementing a deprescribing plan for specific drug classes. Maas et al. [262] also described increased self-efficacy for physical therapists following guideline exposure and peer feedback. Cloutier et al. [263] highlighted increased physician self-efficacy following a multi-faceted guideline implementation but no corresponding change in the desired behaviour. This highlights the importance that eye care practitioners need to regularly use the CDMA when providing nutritional advice to patients with or at risk of AMD so that they familiarise themselves on the usage, as repeated use lends itself to mastery and is consistent with Bandura's theory[264] that such experiences contribute to self-efficacy.

This study has proven the efficacy of a CDMA in the form of a flowchart that was developed by Stevens et al. [213] when providing nutritional advice to patients with or at risk of AMD. The efficacy was tested using self-efficacy surveys and it has shown to increase confidence and self-efficacy scores among fully registered and student optometrists when providing nutritional advice to AMD patients in simulated case scenarios. In addition, the number of correct answers (appropriate nutritional advice to each case scenario) increased significantly with the use of the CDMA. In the next chapter, a summary of the findings of the three studies conducted in this thesis will be discussed, including the limitations for each study and recommendations for future research.

Chapter Six: Discussion

6.1 Summary

AMD is a multi-factorial eye condition affecting those aged 50 years and above. With the increasing greying population in developed countries and also in Singapore, the prevalence of AMD will increase concurrently. Other than being multi-factorial, the exact pathogenesis of AMD is also unknown, but recent research has found oxidative stress to be one of the major contributory factors. As there are currently no treatment available for atrophic AMD, reducing the amount of reactive oxygen intermediates (ROIs) that are produced via oxidative stress is one of the methods to prevent atrophic AMD from progressing to the more advanced stages or to neovascular AMD. ROIs can be scavenged with anti-oxidants such as vitamins A, C and E and substances such as lutein, zeaxanthin and polyunsaturated fatty acids (omega-3 and 6) have also shown to be protective against AMD as discussed in previous chapters.

Study One: Nutritional and smoking advice to patients with or at risk of AMD by Singapore optometrists

The first study "Nutritional and smoking advice to patients with or at risk of AMD by Singapore optometrists" is the first to systematically investigate the extent to which optometrists in Singapore provide advice on modifiable risk factors for AMD. The response rate of this study is 18.2%, similar to Lawrenson and Evan's[209] study with a response rate of 16.2% for the optometrists. Data from Singapore's Optometrists and Opticians Board (OOB) shows that approximately 20% of the Singapore optometrists are degree-trained and 60% of these optometrists are working in retail sector. From our study, almost 40% of the respondents are degree-trained and 60% are working in the retail sector (retail optical shops and clinical optical shops). The percentage of degree-trained optometrists are over-represented in our study but the percentage of optometrists working in retail sector matches the statistic provided by OOB. Attempts were made to obtain more demographic information such as gender and years of experience on

Singapore optometrists from OOB but to no avail, therefore we were unable to establish further on whether the demographics of the respondents are representative of the fully registered optometrists practicing in Singapore. In the UK[209], 67.9% of the optometrists provide dietary advice to patients with advanced AMD most of the time, 52.9% of the Singapore optometrists do that and 28% of the optometrists in Sweden[208] do the same. One of the main reasons Singapore optometrists are not providing dietary advice to patients with advanced AMD is because they seldom see such patients. For patients considered to be at risk of AMD, 53.6% of optometrists in the UK[209] provide dietary advice most of the time, while 31.7% and 25% of the optometrists in Singapore and Sweden[208] respectively provide dietary advice most of the time. 80% of the optometrists in Singapore will advise patients with early, advanced or at risk of AMD to consume green leafy vegetables; most will advise patients to consume daily but did not advise on the amount to consume. Approximately 60% of the optometrists in Singapore will advise patients with early, advanced or at risk of AMD to consume oily fish; most will advise patients to consume daily and will either not advise on the amount or advise patients to consume one serving.

42.3% of optometrists in Singapore will take a smoking history in new or first time patients most of the time and 32.3% and 17% of optometrists in the UK[209] and Sweden[208] respectively will do the same. Conversely, a slightly lesser percentage of optometrists in Singapore (16.5%) will take a smoking history in non-first time or review patients as compared to the optometrists in the UK[209] (21.2%). Slightly more than one third of the optometrists in Singapore will inform smokers of the link between smoking and AMD most of the time and almost half of the optometrists in the UK[209] will advise smokers of the link most of the time. On the other hand, slightly more than half of the optometrists in Singapore will advise AMD patients to stop smoking most of the time and slightly more than a third of the optometrists in the UK[209] will advise AMD patients to stop smoking. While not many optometrists in Singapore will advise smokers of the link between smoking and AMD, a considerable percentage of them will advise them to stop smoking

and this could imply that Singapore optometrists are concerned of the health risks that smoking can bring to their patients.

For all case scenarios except for case scenario two (65 year old patient with advanced AMD in one eye and early AMD in the other), a higher percentage of optometrists in Singapore will recommend supplements as compared to optometrists in the UK[209] and Sweden[208]. The percentage of Singapore optometrists recommending supplements for case scenario two is similar to the percentage of optometrists in the UK[209] who will recommend supplements. In case scenario one, most optometrists in Singapore and UK[209] would recommend supplements containing antioxidant vitamins, lutein and zeaxanthin. In case scenarios two and three, most optometrists in Singapore would recommend AREDS 2 but most optometrists in the UK would recommend a supplement containing macular carotenoids.

There is no difference in self-efficacy scores between optometrists with different years of experience. Nonetheless, there is a significant difference in self-efficacy scores for almost all statements between optometrists working in retail and optometrists working in clinical setting, as well as between optometrists with a Diploma and optometrists with higher qualification. The only statement that did not show a significant difference is “I am confident that I can advise a patient with AMD on the quantities of food that might be beneficial for their eye health.” This shows that regardless of practice setting or qualification, most optometrists in Singapore are not too confident when advising AMD patients on the quantities of food that might be beneficial for their eye health.

Study Two: What do Singapore optometrists feel about providing nutritional and smoking advice to patients with or at risk of AMD?

From this qualitative research, all the optometrists who were interviewed think that nutrition is beneficial for the eye health and the two most common conditions that they provide nutritional advice to their patients are AMD and dry eyes. Nonetheless, most optometrists do not provide further information on the amount and frequency of food or

supplement that they recommended to their patients. All optometrists felt positive about providing nutritional advice to their patients and some felt that it could help to differentiate them from other optometrists who are not providing such advice. From the optometrists' view, they felt that patients are generally quite receptive on optometrists providing them with nutritional advice, even though there may be a few who felt that providing nutritional advice is not within the job scope of optometrists in Singapore. Besides the eye condition, stage and/or risk factors of the condition, the other factors that determine whether Singapore optometrists provide nutritional advice include patient receptiveness, as well as presence of other systemic conditions or medications that the patient is currently taking. As such, Singapore optometrists find it challenging to provide nutritional advice to AMD patients as they feel that their knowledge in this area is insufficient to provide such advice. In addition, many members of the public in Singapore are still unaware of the capabilities of optometrists; that they are proficient in performing many eye tests to diagnose eye diseases and manage them appropriately. To further support Singapore optometrists, their capabilities should be made known to more members of the public so that they could perform a comprehensive eye examination on every patient. Additionally, optometrists felt that they need a guideline when providing nutritional advice to AMD patients so that they can be more assured that the advice that they provide are accurate and based on the most recent research results.

Study Three: Evaluation of a CDMA for qualified and student optometrists when providing nutritional advice for patients with or at risk of AMD

In this interventional study, the efficacy of a CDMA was evaluated among qualified and student optometrists and the results show that the self-efficacy scores for both groups of optometrists were improved significantly after using the CDMA. Furthermore, the number of correct answers for the hypothetical case scenarios increased significantly after using the CDMA for both qualified and student optometrists. This shows that the CDMA is

beneficial for qualified and student optometrists when providing nutritional advice to AMD patients.

6.2 Conclusions

With the increasing greying population in Singapore, the prevalence of AMD will increase, but this condition could be undiagnosed unless patient's vision has been affected or if patient go for a comprehensive eye examination regularly. Therefore, optometrists, especially those working in the retail optical shops, should routinely perform fundus examination on all patients aged 50 and above in order to diagnose AMD early. On the other hand, the general public in Singapore needs to have a much better understanding on optometrists' roles and capabilities. Singapore optometrists need to perform more comprehensive eye examinations in order to diagnose more AMD patients so that they could give nutritional advice to these patients before their conditions start to deteriorate. Whilst not a big percentage of Singapore optometrists routinely take a smoking history on new and review patients and inform smokers of the link between smoking and AMD, about half of them would advise AMD patients to stop smoking and more optometrists should routinely take a smoking history on all patients and advise AMD patients who are currently smoking to quit smoking as smoking is strongly related to AMD. Singapore optometrists could adopt the 3A1R protocol: "Ask about smoking, Advise to quit, Assess willingness to quit, Refer to tobacco quitlines" as it has been shown to effectively improve eye care practitioners' smoking cessation counseling practices in the U.S[265].

Singapore optometrists believe in nutrition and the eye, especially for AMD but they feel that they lack the knowledge to provide nutritional advice for AMD patients. As a starting point to explore further in this area, they could utilize the CDMA that was evaluated in this study, as it has been shown to be beneficial for optometrists in Singapore as well as in the UK[213]. Alternatively, Singapore optometrists could also consider to co-manage AMD patients in this area with pharmacists or ophthalmologists if they do not feel too confident in providing nutritional advice to AMD patients. In conclusion, optometrists in

Singapore should be providing nutritional and smoking advice to more AMD patients as currently this is the most feasible option and with the projected increasing prevalence of AMD in the years to come, this will be the best option. One of the ways to encourage Singapore optometrists to provide nutritional and smoking advice to more AMD patients is through continuing professional education seminars to increase their knowledge and hence confidence when providing such advice to their patients. Another alternative method is to publish these results for Singapore optometrists to be more aware of the current situation in Singapore.

6.3 Limitations and recommendations for future research

Study One: Nutritional and smoking advice to patients with or at risk of AMD by Singapore optometrists

Despite having a good response rate of 18.2% in this study, the demographics of respondents represent more degree-trained optometrists as almost 40% of the respondents are degree-trained, whereas statistics from OOB state that approximately 20% of Singapore optometrists are degree-trained. Therefore, more responses from optometrists with a diploma qualification should be included. The use of questionnaire in this study is subject to response and recall bias, and as shown in the response rate, there were 217 respondents initially via the Survey Monkey platform but only 111 completed the questionnaire as those who did not complete might feel that they are not too familiar with the topic of nutrition and AMD, or this area is not quite relevant to their practice. All the responses for this questionnaire was made anonymous to protect the identities of the respondents, but this could result in possible duplications of responses from the same respondent. However, this has been looked into prior to data analysis as the principal researcher manually browsed through all the respondents' demographics to ensure there are no duplications. As AMD patients are mostly seen by ophthalmologists in Singapore, future research could recruit ophthalmologists to share their views on nutrition and AMD.

Study Two: What do Singapore optometrists feel about providing nutritional and smoking advice to patients with or at risk of AMD?

In this study, the optometrists were recruited from different practices: retail optical shops, clinical optical shops, institutions and eye hospitals or eye clinics and there was not much difference in their views and opinions. For future research, more optometrists with diploma qualification should be recruited as about 80% of optometrists in Singapore graduated with a diploma in optometry, and their opinions could be compared with the optometrists with higher qualifications. Besides, more could be explored from optometrists the reason(s) behind recommending a particular supplement for their AMD patients as this has not been fully established from this study.

Study Three: Evaluation of a CDMA for qualified and student optometrists when providing nutritional advice for patients with or at risk of AMD

The CDMA has shown to be beneficial for both qualified and student optometrists in this study but it will be even more significant if the qualified optometrists were to use it in their practices, as case scenarios will not be able to replace real-life clinical situations. Furthermore, it will be more ideal if the sample size in the non-experienced group could be increased to 27 (the sample size required following GPower calculation), even though the results in this study has proven to be significant. This thesis also highlights the need to educate Singapore optometrists about discussing smoking cessation with their patients. For future research, an evidence-based smoking cessation protocol could be tested with Singapore optometrists to evaluate if it will increase and improve smoking cessation counselling practice.

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Appendices:

Appendix A

Survey on nutritional and smoking advice to patients with or at risk of age-related macular degeneration (AMD) by optometrists in Singapore

Kindly answer all questions, based on your practice as an optometrist in Singapore.

Section 1: Demographic Information

Your current age:	
Gender:	
Number of years practicing as a fully registered optometrist:	
Highest qualification attained in the field of optometry:	Diploma/ Advanced diploma/ Bachelor/ Masters/ PhD/ Others _____ (Circle one)
Type of practice (A):	Retail optical shop/ Clinical (Includes hospitals and eye clinics)/ Clinical optical shop* (Circle one)
Type of practice (B):	Independent or Private/ Chain/ Government (Circle one)
Location of current practice (A):	North/ South/ East/ West/ Central (Circle one)
Location of current practice (B):	Shopping malls/ Neighbourhood areas/ Hospitals/ Eye clinics/ Institutions (Schools) (Circle one)

Your practice is defined as **clinical optical shop if slit-lamp examination and ophthalmoscopy is routinely performed on all patients/ customers*

Section 2: Tests routinely performed on patients/ customers aged 50 and above

2.1 Average number of patients/ customers aged 50 and above seen **per week** in your practice:

_____

2.2 Which of the following tests are routinely performed on patients/ customers aged 50 and above in your practice? (You may tick more than one)

- History taking
- Objective refractive
- Subjective refraction
- Pupillary assessment
- Ocular motility
- Cover test
- Confrontation
- Colour vision assessment
- Anterior segment examination (Slit-lamp bio-microscopy)

- Poster segment examination (Fundus examination)
- Tonometry
- Others (please specify)

  _____
  _____

Section 3: Number of AMD patients/ customers seen per year

3.1 Average number of patients/ customers seen with category 1 or 2* AMD **per year**:

_____

**Category 1: less than 5 small drusen (<63 microns: approximately the width of a retinal artery near the optic nerve head)*
Category 2: multiple small drusen or nonextensive intermediate drusen (63-124 microns), pigment abnormalities, or a combination of the two (refer to appendix A for sample images)

3.2 Average number of patients/ customers seen with category 3 or 4* AMD **per year**:

_____

**Category 3: no advanced AMD but had ≥ 1 large drusen (125 microns), extensive area of intermediate drusen, or geographic atrophy (GA) not involving the center of macula*
Category 4: advanced AMD, central GA or neovascular AMD in one eye (refer to appendix A for sample images)

Section 4: Perspective on AMD and nutrition

4.1 Are you aware of the link between AMD and nutrition?
- Yes
- No

4.2 Is your nutritional advice to patients/ customers with or at risk of AMD restricted by your current practice?
- Yes
- No

Section 5: Dietary advice to patients/ customers with early (category 1 or 2) AMD

5.1 Frequency of dietary advice for patients/ customers with **early (category 1 or 2) AMD**
- Never
- Rarely (10% of the time)
  - What is/ are your main reason(s) for not/rarely advising?
    - Insufficient evidence that nutrition is beneficial for patients/ customers with category 1 or 2 AMD
    - Do not believe that nutrition is beneficial for patients/ customers with category 1 or 2 AMD
    - Not aware that nutrition is beneficial for patients/customers with category 1 or 2 AMD
    - Insufficient time
    - Rarely see category 1 or 2 AMD cases
    - Others:

      _____
      _____

- Sometimes (20-40% of the time)
- Often (50-70% of the time)
- Most of the time (80-90% of the time)
- Always (100% of the time)

5.2 Kindly indicate if the following dietary advice was provided for patients/ customers with **early (category 1 or 2) AMD**

- Eat plenty of leafy green vegetables

  Frequency: _____ (Advised to consume daily, once a week, etc., or not mentioned)

  Amount: _____ (Please indicate if it is in servings, grams, others, or not mentioned)

- Eat oily fish, such as salmon

  Frequency: _____ (Advised to consume daily, once a week, etc., or not mentioned)

  Amount: _____ (Please indicate if it is in servings, grams, others, or not mentioned)

- Other: _____

  Frequency: _____ (Advised to consume daily, once a week, etc., or not mentioned)

  Amount: _____ (Please indicate if it is in servings, grams, others, or not mentioned)

5.3 Do you think that optometrists in Singapore should be providing dietary advice to patients/ customers with **early (category 1 or 2) AMD**?

- Yes
- No (Kindly state reason)

  _____
  _____

Section 6: Dietary advice to patients/ customers with advanced (category 3 or 4) AMD

6.1 Frequency of dietary advice for patients/ customers with **advanced (category 3 or 4) AMD**

- Never
- Rarely (10% of the time)
  - What is/ are your main reason(s) for not/rarely advising?
    - Insufficient evidence that nutrition is beneficial for patients/ customers with category 3 or 4 AMD
    - Do not believe that nutrition is beneficial for patients/ customers with category 3 or 4 AMD
    - Not aware that nutrition is beneficial for patients/customers with category 3 or 4 AMD
    - Insufficient time

- Rarely see category 3 or 4 AMD cases
- Others:

  _____

  _____

- Sometimes (20-40% of the time)
- Often (50-70% of the time)
- Most of the time (80-90% of the time)
- Always (100% of the time)

6.2 Kindly indicate if the following dietary advice was provided for patients/ customers with **advanced (category 3 or 4) AMD**

- Eat plenty of leafy green vegetables

  Frequency: _____ (Advised to consume daily, once a week, etc., or not mentioned)

  Amount: _____ (Please indicate if it is in servings, grams, others, or not mentioned)

- Eat oily fish, such as salmon

  Frequency: _____ (Advised to consume daily, once a week, etc., or not mentioned)

  Amount: _____ (Please indicate if it is in servings, grams, others, or not mentioned)

- Other: _____

  Frequency: _____ (Advised to consume daily, once a week, etc., or not mentioned)

  Amount: _____ (Please indicate if it is in servings, grams, others, or not mentioned)

6.3 Do you think that optometrists in Singapore should be providing dietary advice to patients/ customers with **advanced (category 3 or 4) AMD**?

- Yes
- No (Kindly state reason)

  _____

  _____

Section 7: Dietary advice to patients/ customers considered to be at risk of AMD

7.1 Frequency of dietary advice for patients/ customers considered to be **at risk of AMD**

- Never
- Rarely (10% of the time)
  - What is/ are your main reason(s) for not/rarely advising?
    - Insufficient evidence that nutrition is beneficial for patients/ customers at risk of AMD
    - Do not believe that nutrition is beneficial for patients/ customers at risk of AMD

- Not aware that nutrition is beneficial for patients/customers at risk of AMD
- Insufficient time
- Rarely see patients/ customers at risk of AMD
- Others:

  _____

  _____

- Sometimes (20-40% of the time)
- Often (50-70% of the time)
- Most of the time (80-90% of the time)
- Always (100% of the time)

7.2 Kindly indicate if the following dietary advice was provided for patients/ customers considered to be **at risk of AMD**

- Eat plenty of leafy green vegetables

  Frequency: _____ (Advised to consume daily, once a week, etc., or not mentioned)

  Amount: _____ (Please indicate if it is in servings, grams, others, or not mentioned)

- Eat oily fish, such as salmon

  Frequency: _____ (Advised to consume daily, once a week, etc., or not mentioned)

  Amount: _____ (Please indicate if it is in servings, grams, others, or not mentioned)

- Other: _____

  Frequency: _____ (Advised to consume daily, once a week, etc., or not mentioned)

  Amount: _____ (Please indicate if it is in servings, grams, others, or not mentioned)

7.3 Do you think that optometrists in Singapore should be providing dietary advice to patients/ customers considered to be **at risk of AMD**?

- Yes
- No (Kindly state reason)

  _____

  _____

Section 8: Smoking and AMD

8.1 Are you aware that smoking is a risk factor of AMD?

- Yes
- No

8.2 Frequency of taking a smoking history in **new or first time patients/ customers**

- Never
- Rarely (10% of the time)
- Sometimes (20-40% of the time)
- Often (50-70% of the time)
- Most of the time (80-90% of the time)
- Always (100% of the time)

8.3 Frequency of taking a smoking history in **non-first time review patients/ customers**

- Never
- Rarely (10% of the time)
- Sometimes (20-40% of the time)
- Often (50-70% of the time)
- Most of the time (80-90% of the time)
- Always (100% of the time)

8.4 Frequency of informing smokers of the link between smoking and AMD

- Never
- Rarely (10% of the time)
- Sometimes (20-40% of the time)
- Often (50-70% of the time)
- Most of the time (80-90% of the time)
- Always (100% of the time)

8.5 Frequency of advising patients/ customers **with AMD** to stop smoking

- Never
- Rarely (10% of the time)
- Sometimes (20-40% of the time)
- Often (50-70% of the time)
- Most of the time (80-90% of the time)
- Always (100% of the time)

8.6 Frequency of advising patients/ customers **at risk of AMD** to stop smoking

- Never
- Rarely (10% of the time)
- Sometimes (20-40% of the time)
- Often (50-70% of the time)
- Most of the time (80-90% of the time)
- Always (100% of the time)

Section 9: Recommendations on nutritional supplements in patients with established or at risk of developing AMD

Kindly indicate the type of supplements (if any) that will be recommended to your patients/ customers based on the following scenarios during your practice.

Scenario 1:

55 year old patient with no evidence of AMD but with one or more parents and/or siblings affected by AMD

- NO supplement recommended
- AREDS formula
- AREDS 2 formula
- Supplements containing macular carotenoids

- Supplements containing antioxidant vitamins, lutein and zeaxanthin
- Supplements containing omega 3 fatty acids
- Others (please specify)

_____

Scenario 2:
65 year old patient with advanced AMD in one eye and early AMD in the other

- NO supplement recommended
- AREDS formula
- AREDS 2 formula
- Supplements containing macular carotenoids
- Supplements containing antioxidant vitamins, lutein and zeaxanthin
- Supplements containing omega 3 fatty acids
- Others (please specify)

_____

Scenario 3:
75 year old patient with advanced AMD in both eyes

- NO supplement recommended
- AREDS formula
- AREDS 2 formula
- Supplements containing macular carotenoids
- Supplements containing antioxidant vitamins, lutein and zeaxanthin
- Supplements containing omega 3 fatty acids
- Others (please specify)

_____

9.2 Would you consider the smoking status or history of your patients/ customers when recommending nutritional supplements?

- Yes
- No

9.3 Which of the following sources of evidence provide you with information on nutritional supplements and AMD? (You may tick more than one)

- Articles in professional journals
- Conference presentations, CPE events
- Reference to specific studies, eg. AREDS
- Scientific/ Research literature
- Manufacturers literature
- Expert opinion
- Others (please specify)

_____

Section 10: Confidence in classifying AMD and providing nutritional advice to patients with or at risk of AMD

Kindly rate your confidence level from 0 to 100 (**in 10 increment steps**) for the following statements.

(0=least confident, 100=most confident)

		0 = least confident; 100 = most confident
10.1	I am confident that I could classify the type of AMD a patient has based on retinal signs.	
10.2	I am confident that I can advise a patient with AMD on the relationship between AMD and nutrition.	
10.3	I am confident that I can advise a patient with AMD on what foods to eat that might be beneficial for their condition.	
10.4	I am confident that I can advise a patient with AMD on the quantities of food that might be beneficial for their eye health.	
10.5	I am confident that I can advise a patient with AMD on when nutritional supplementation may be beneficial.	
10.6	I am confident that I can advise a patient with AMD on what supplements to take and what dosage to recommend.	
10.7	I am confident with talking about nutrition to those at risk of AMD.	

Would you be interested to participate in evaluating a clinical decision making aid for advising patients with or at risk of AMD?

Yes / No

If yes, kindly fill in the following:

Email address:_____

Contact number: _____

- Thank you for your participation -

Appendix B

13 October 2017

[redacted]

RE: Invitational letter to participate in research study titled: "Nutritional and smoking advice given to patients with or at risk of age-related macular degeneration by optometrists in Singapore

Dear fellow optometrist,

As we are all aware, Singapore has a rapidly greying population and with this trend, the prevalence of age-related macular degeneration (AMD) is expected to increase. While treatment is currently available for wet AMD, there is no treatment for dry or moderate AMD and the only available and most appropriate option is to target the modifiable factors such as diet and smoking.

As part of my PhD research study, I would like to understand the nutritional and smoking advice that is given by you, as an eye-care professional to your patients with or at risk of AMD. More information on the research study can be found in the attached "Study Information-Phase 1" document.

Therefore I would really appreciate if you could spend approximately fifteen minutes of your time to complete the attached questionnaire, together with the signed informed consent form, and mail it back to me in the return envelope.

Alternatively, if you prefer to complete this questionnaire online, you may access it via this website: [redacted]

Kindly complete the questionnaire only once, latest by 31 March 2018.

I look forward to your response and feel free to contact me at [redacted] should you have any questions on the research study.

Thank you for your time.

Warmest regards,

Stacy Chan Hsiao Lan
Diploma in Optometry (Singapore Polytechnic, 2003)
Bachelor of Optometry (University of Auckland, 2008)

Appendix C

Aston University
Life & Health Sciences

STUDY INFORMATION – Phase 1

Version Five 13/10/17

Nutritional and smoking advice given to patients with or at risk of age-related macular degeneration by optometrists in Singapore

Purpose of the study

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness registration in the developed world and in countries with an ageing population such as Singapore, the prevalence of AMD is expected to rise. While the treatment for "wet" AMD seems promising, there is currently no treatment available for "dry" AMD, and the only available and most appropriate option is to target the modifiable factors such as diet and smoking. The results from AREDS 1 and AREDS 2 have shown that the intake of antioxidants such as vitamins E and C, beta-carotene or lutein and zeaxanthin and zinc could reduce the risk of developing advanced AMD. Additionally, there is also increasing evidence that smoking is casually linked to the development of AMD.

This study consists of two phases and this study information relates to Phase 1. In Phase 1 of this study, we aim to investigate the nutritional and smoking advice that optometrists in Singapore are currently providing to their patients with or at risk of AMD through a questionnaire. At the end of the questionnaire, you will be asked to indicate your interest to participate in Phase 2 of this study, which is to evaluate the effectiveness of a clinical decision-making aid.

Why have I been chosen?

This study is open to any optometrist who is fully registered under the Optometrists and Opticians Board (OOB) and is currently practicing in Singapore.

Do I have to take part?

No, you do not have to participate if you do not wish to do so. If you decide to participate, you are free to withdraw from the study at any time without penalty.

What does the study involve?

You will be requested to complete a questionnaire on AMD either through an online link or on hardcopy, and this questionnaire will take approximately fifteen minutes of your time.

The questionnaire includes the following questions:

- Demographic information including age, gender, number of years practicing as a fully registered optometrist, highest qualification attained in the field of optometry as well as the type and location of practice currently working in.
- Tests routinely performed on patients aged 50 and above (2 questions)
- Number of AMD patients seen per year (2 questions)
- Perspective on AMD and nutrition (2 questions)
- Dietary advice to patients with early (Category 1 or 2) AMD (3 questions)
- Dietary advice to patients with advanced (Category 3 or 4) AMD (3 questions)
- Dietary advice to patients considered to be at risk of AMD (3 questions)
- Smoking and AMD (6 questions)
- Recommendations on nutritional supplements in patients with established or at risk of developing AMD (5 questions)
- Confidence in classifying AMD and providing nutritional advice to patients with or at risk of AMD (7 questions)

At the end of the questionnaire, you will be invited to indicate if you would like to participate in Phase 2 of this study, that is to validate a clinical decision making aid when providing nutritional advice for patients with or at risk of AMD. If interested, you will be asked to provide your contact details.

What are the benefits of taking part?

It is anticipated that the results in this study can help to identify the areas that optometrists in Singapore are lacking in when providing nutritional and smoking advice to patients with or at risk of AMD, and subsequently be trained on these areas during conferences or continuing professional education seminars.

Are there any risks or disadvantages of taking part?

This study does not involve any known physical risks and optometrists are requested to spend approximately fifteen minutes of their time to complete the questionnaire and to mail it should they choose to complete the hardcopy version. There is a risk of breaching privacy and confidentiality in relation to your survey results but this risk will be minimised by keeping your data anonymous at all times. Ms. Stacy Chan will be responsible for putting your survey results onto a database and maintaining your privacy and confidentiality. Only Ms. Stacy Chan will have access to the database that is password protected.

What will happen to the results of the study?

We aim to publish the results of this research study. However, there will be no reference to any optometrist's survey results in any publication. A copy of the published research will be provided to you once the research study has been approved for publishing.

Who has reviewed the study?

The study has been reviewed by Aston University Research Ethics Committee and Parkway Independent Ethics Committee.

Researchers

Stacy Hsiao Lan Chan

Optometrist, Doctorate of Optometry student. Vision Sciences department, Aston University

Contact: [redacted]

Hannah Bartlett

Optometrist. Senior Lecturer. Vision Sciences department, Aston University.

Contact: [redacted]

Where can I get more information?

Please contact Rebekah Stevens [redacted] if you would like any more information about the study.

What if there is a problem?

If you have any concerns about anything to do with this study, you should speak to the research team and they will do their best to answer your concerns. You may contact either Stacy Chan at [redacted], or Hannah Bartlett at [redacted] telephone 0121 204 4182. If they cannot help you and you still have concerns or wish to make a complaint about the way in which the study has been conducted, then you should contact the Aston University Director of Governance, [redacted].

Appendix D

Aston University
Life & Health Sciences

CONSENT FORM (PHASE 1)

Version 4: 13 October 2017

Project Title: Nutritional and smoking advice given to patients with or at risk of age-related macular degeneration (AMD) by optometrists in Singapore

Name of Researcher(s): Hannah Bartlett and Stacy Chan

		Initial
1	I confirm that I have read and understand the information sheet (Version 5 dated 13 October 2017) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.	
3	I agree to take part in the above study.	

Name of volunteer	Signature of volunteer	Date

Name of researcher	Signature of researcher	Date

Appendix E

Appendix A: Sample images for AMD categorization

Category 2: multiple small drusen or nonextensive intermediate drusen (63-124 microns), pigment abnormalities, or a combination of the two

Category 3: no advanced AMD but had ≥ 1 large drusen (125 microns), extensive area of intermediate drusen, or geographic atrophy (GA) not involving the center of macula

Category 4: advanced AMD, central GA or neovascular AMD in one eye

Appendix F

Dear fellow optometrist,

As we are all aware, Singapore has a rapidly greying population and with this trend, the prevalence of age-related macular degeneration (AMD) is expected to increase. While treatment is currently available for wet AMD, there is no treatment for dry or moderate AMD and the only available and most appropriate option is to target the modifiable factors such as diet and smoking.

As part of my PhD research study, I would like to understand the nutritional and smoking advice that are given by you, as an eye-care professional to your patients with or at risk of AMD. More information on the research study can be found here. (Link to Study Information-Phase 1 document)

Therefore I would really appreciate if you could spend fifteen minutes of your time to complete a questionnaire by clicking on this link. (Link to consent form and questionnaire) Kindly complete the questionnaire only once.

I look forward to your response and feel free to contact me at [redacted] should you have any questions on the research study.

Thank you for your time.

Appendix G

PRIVATE & CONFIDENTIAL

Parkway Pantai

[redacted]

PIEC Ref: P[redacted]

31 October 2017

[redacted]

Dear Ms Chan

APPROVAL OF STUDY AMENDMENTS

Study Title: Nutritional and smoking advice given to patients with or at risk of age-related macular degeneration by optometrist in Singapore

We are pleased to inform you that the Parkway Independent Ethics Committee (PIEC) has reviewed and approved the amendments for the research study as titled above under expedited review.

All forms and guidelines can be accessed from [redacted]

PIEC may conduct an audit of the research at any time.

Should you have any queries pertaining to the requirements or determinations of PIEC, please contact PIEC office on [redacted]

Yours sincerely,

[redacted]

Parkway Independent Ethics Committee

Encl: Appendix A: Documents reviewed and noted

The Parkway Independent Ethics Committee is constituted and operates in accordance with the ICH GCP, the Standard Operating Procedures for PIEC and all applicable laws and regulations.

[redacted]

Appendix A

Documents Reviewed and Noted

S/N	Documents reviewed	Version No.	Date
1	PIEC Study Amendment Cover Note	-	23-Oct-2017
2	Research Protocol	5.0	21-Aug-2017
3	Appendix A: Samples images for AMD categorization	1.0	23-Aug-2017
4	Study Information – Phase 1	6.0	31-Oct-2017
5	Consent Form (Phase 1)	5.0	31-Oct-2017
6	Study Information – Phase 2	7.0	31-Oct-2017
7	Consent Form (Phase 2)	5.0	31-Oct-2017
8	Invitation Letter	4.0	13-Oct-2017
9	Survey Form	6.0	23-Aug-2017

S/N	Documents Noted	Version No.	Date
1	NIL		

It is the responsibility of each Site Principal Investigator to ensure that the translated documents are an accurate reflection of the English version approved by PIEC.

If the document has no version date listed, one will be created for you. Please ensure the footer of these documents are updated to include this version date prior to use to ensure ongoing version control.

Parkway Pantai

PRIVATE & CONFIDENTIAL

[redacted]

Ref: **PIEC/2017/004**

28 May 2018

Ms Chan Hsiao Lan Stacy
[redacted]

Dear Ms Chan,

RENEWAL OF PIEC APPROVAL

Study Title: Nutritional and smoking advice given to patients with or at risk of age-related macular degeneration by optometrist in Singapore

We are pleased to inform you that the Parkway Independent Ethics Committee (PIEC) has renewed the approval for the research study as titled above, being conducted in the following study sites(s) under expedited review:

- Aston University, Singapore-based Researcher (PhD Program):
  - Site PI: Ms Chan Hsiao Lan Stacy
  - Collaborator: Dr Hannah Bartlett

The approval period is from **29 May 2018** to **28 May 2019**.

Continued approval is conditional upon your compliance with the following requirements:

1. Only the approved Participant Information Sheet and Consent Form should be used. It must be signed by each subject prior to initiation of any protocol procedures. In addition, each subject should be given a copy of the signed consent form.
2. No deviation from, or changes to, the protocol should be implemented without documented approval from the PIEC, except where necessary to eliminate apparent immediate hazard(s) to the study subjects, or when the change(s) involves only logistical or administrative aspects of the research.
3. Any deviation from protocol, any changes to the protocol or study to eliminate an immediate hazard, including premature termination, should be promptly reported to the PIEC within seven (7) calendar days.

[redacted]

COMPANY REG. NO. 200409811Z

4. Please submit the following to the PIEC:

   a. All Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSOs) must be reported to the PIEC. All problems involving death of a local subject, regardless of the causality and expectedness, must be reported within 24 hours after first knowledge by the Site Principal Investigator. All other problems must be reported as soon as possible but not later than seven (7) calendar days after first knowledge by the Principal Investigator.

   b. Any proposed amendments to the study, including any changes to the Protocol/ Investigator's Brochure, Participant Information Sheet and Consent Form, any other study materials that are intended to be read or received by the subjects or potential subjects or the study team.

   c. Report(s) on any new information that may adversely affect the safety of the subject or the conduct of the study.

   d. Continuing Review – The PIEC Study Status Report Form is to be submitted at least 4 weeks prior to expiry of the approval period. Please take note of the submission deadline for full board review, if applicable. The study cannot continue beyond the expiration date, **28 May 2019** until approval is renewed by the PIEC. Expiration date is the last date that the study is approved.

   e. Study Closure – The PIEC Study Status Report Form is to be submitted as the Final Study Status Report within 4 weeks of study closure.

All forms and guidelines can be accessed from [redacted]

PIEC may conduct an audit of the research at any time.

Should you have any queries pertaining to the requirements or determinations of PIEC, please contact PIEC office on +[redacted]

Yours sincerely,

[redacted]
Parkway Independent Ethics Committee

Encl: Appendix A: Documents reviewed and noted

The Parkway Independent Ethics Committee is constituted and operates in accordance with the ICH GCP, the Standard Operating Procedures for PIEC and all applicable laws and regulations.

Appendix A
Documents Reviewed and Noted

S/N	Documents reviewed	Version No.	Date
1	PIEC Study Status Report Form	-	07-May-2018

S/N	Documents Noted	Version No.	Date
1	NIL		

It is the responsibility of each Site Principal Investigator to ensure that the translated documents are an accurate reflection of the English version approved by PIEC.

If the document has no version date listed, one will be created for you. Please ensure the footer of these documents are updated to include this version date prior to use to ensure ongoing version control.

Appendix H

Aston University
Life & Health Sciences

STUDY INFORMATION – Phase 1b

Version One – 05/02/19

Nutritional and smoking advice given to patients with or at risk of age-related macular degeneration by optometrists in Singapore

Purpose of the study

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness registration in the developed world and in countries with an ageing population such as Singapore, the prevalence of AMD is expected to rise. While the treatment for "wet" AMD seems promising, there is currently no treatment available for "dry" AMD, and the only available and most appropriate option is to target the modifiable factors such as diet and smoking. The results from AREDS 1 and AREDS 2 have shown that the intake of antioxidants such as vitamins E and C, beta-carotene or lutein and zeaxanthin and zinc could reduce the risk of developing advanced AMD. Additionally, there is also increasing evidence that smoking is casually linked to the development of AMD.

This study consists of two phases and this study information relates to Phase 1b. In Phase 1b of this study, we aim to understand optometrists' views on nutrition and the eye via a face-to-face interview.

Why have I been chosen?

This study is open to any optometrist who is fully registered under the Optometrists and Opticians Board (OOB) and is currently practicing in Singapore.

Do I have to take part?

No, you do not have to participate if you do not wish to do so. If you decide to participate, you are free to withdraw from the study at any time without penalty.

What does the study involve?

You will go through a face-to-face interview with the main researcher, Stacy Chan, and this interview will take approximately thirty to forty-five minutes of your time at a location of your convenience.

The interview will include the following questions:

- Do you think nutrition plays a role in preventing or treating certain eye conditions? What are the eye conditions that you think will benefit from nutrition? (*For each eye condition, what nutritional advice/information have you given to patients? Or for each eye condition, what kind of nutritional advice/information do you think is appropriate for patients?*) Where do you get the information regarding nutrition and the eye from?

- What were your patients' reactions to you offering this advice/information? (*If participants have not engaged in this scenario, ask whether participants believe that patients would expect optometrists to be involved in this type of activity and why?)*
- How do you feel about including nutritional advice/information within your patient management?
- What factors influence whether or not you give nutritional advice/information to your patients? What do you think is most challenging/difficult when providing nutritional/ smoking advice to AMD patients?
- Do you routinely screen for age-related macular degeneration (AMD) in your practice for patients aged 50 years and above? (*If yes, ask how is AMD diagnosed in your practice? If no, ask what is/are the main reasons for not routinely screening?)* Currently the use of diagnostic drugs has not been legalized in Singapore, but do you think the use of these drugs will aid in your diagnosis of AMD?
- If you agree that you have an important role to play in the health promotion and dietary advice giving to patients, what can be done to support you further in your professional development relating to this aspect of your role?
- Are there any other comments you would like to make in relation to this area of patient care and management?

For analysis of the research data, the entire interview will be voice recorded.

What are the benefits of taking part?

It is anticipated that the results in this study can help to understand Singapore optometrists' view on nutrition and the eye, particularly the areas that optometrists in Singapore are lacking in when providing nutritional and smoking advice to patients with or at risk of AMD. Optometrists in Singapore can then be subsequently trained in these areas during conferences or continuing professional education seminars.

Are there any risks or disadvantages of taking part?

This study does not involve any known physical risks and optometrists are requested to spend approximately thirty to forty-five minutes of their time for the interview. There is a risk of breaching privacy and confidentiality in relation to your survey results but this risk will be minimised by keeping your data anonymous at all times. Ms. Stacy Chan will be responsible for recording the interview, downloading it into a database, and maintaining your privacy and confidentiality. Only Ms. Stacy Chan will have access to the database that is password protected.

What will happen to the results of the study?

We aim to publish the results of this research study. However, there will be no reference to any optometrist's interview results in any publication. A copy of the published research will be provided to you once the research study has been approved for publishing.

Who has reviewed the study?

The study has been reviewed by Aston University Research Ethics Committee and Parkway Independent Ethics Committee.

Researchers

Stacy Hsiao Lan Chan

Optometrist, Doctorate of Optometry student. Vision Sciences department, Aston University

Contact: [redacted]

Hannah Bartlett

Optometrist. Senior Lecturer. Vision Sciences department, Aston University.

Contact: [redacted]

Where can I get more information?

Please contact Rebekah Stevens [redacted] if you would like any more information about the study.

What if there is a problem?

If you have any concerns about anything to do with this study, you should speak to the research team and they will do their best to answer your concerns. You may contact either Stacy Chan at [redacted], or Hannah Bartlett at [redacted] or telephone [redacted]. If they cannot help you and you still have concerns or wish to make a complaint about the way in which the study has been conducted, then you should contact the Aston University Director of Governance, [redacted].

If you want an independent opinion of your rights as a research subject you may contact the Secretariat of Parkway Independent Ethics Committee (PIEC) at [redacted] or [redacted]).

Appendix I

Aston University
Life & Health Sciences

CONSENT FORM (PHASE 1b)

Version 1: 5 February 2019

Project Title: Nutritional and smoking advice given to patients with or at risk of age-related macular degeneration (AMD) by optometrists in Singapore

Name of Researcher(s): Hannah Bartlett and Stacy Chan

		Initial
1	I confirm that I have read and understand the information sheet (Version 1 dated 5 February 2019) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.	
3	I agree to take part in the above study.	

_____	_____	_____
Name of volunteer	Signature of volunteer	Date
_____	_____	_____
Name of researcher	Signature of researcher	Date

Appendix J

Aston University
Life & Health Sciences

STUDY INFORMATION – Phase 2

Version Seven 31/10/17

Nutritional and smoking advice given to patients with or at risk of age-related macular degeneration by optometrists in Singapore

Purpose of the study

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness registration in the developed world. In countries with an ageing population such as Singapore, the prevalence of AMD is expected to rise and following the AREDS 1 study, there were many nutritional supplements available in the market that claimed to preserve the vision of patients with AMD. However, patients or even some optometrists are unaware that the AREDS formulation is only beneficial for patients with moderate AMD. It is important for optometrists to know which patients meet the AREDS inclusion criteria, and could benefit from this specific formulation. Therefore, a clinical decision-making aid has been developed in the form of a flowchart to help optometrists choose the appropriate nutritional advice for their patients.

This study consists of two phases and this study information relates to Phase 2, where the aim is to validate this clinical decision-making aid.

Why have I been chosen?

This study is open to any optometrist who is fully registered under the Optometrists and Opticians Board (OOB) and is currently practicing in Singapore.

Do I have to take part?

No, you do not have to participate if you do not wish to do so. If you decide to participate, you are free to withdraw from the study at any time without penalty.

What does the study involve?

You will be requested to validate a clinical decision-making aid in the form of a flowchart by completing a self-efficacy survey before and after using the aid based on case scenarios.

Firstly, you will be presented with five AMD scenarios and asked to indicate the nutritional advice that you will provide for each case. After which, you will be requested to complete a short survey of seven questions that takes approximately five minutes and will assess your thoughts on giving nutritional advice to patients with or at risk of AMD. The survey will involve answering questions on a scale of 0 – 100.

You will then be provided with the clinical decision-making aid and be briefed on how to use it. The five case scenarios will then be presented to you again and you will be requested to provide the appropriate nutritional advice for each case with the aid. Finally, you will be asked to complete the survey again with the seven questions that will take another five minutes of your time.

Will I be compensated for my participation?

You will be reimbursed with S$10 coffee voucher for participation in this study.

Are there any risks of disadvantages of taking part?

There are minimal potential risks in taking part in this study. Some optometrists may lack confidence in the area of nutrition for AMD but participation is anonymous and their confidence has the potential to improve after using the clinical decision-making aid. There is a risk of breaching privacy and confidentiality in relation to your survey results but this risk will be minimised by keeping your data anonymous at all times. Ms. Stacy Chan will be responsible for putting your survey results onto a database and maintaining your privacy and confidentiality. Only Ms. Stacy Chan will have access to the database that is password protected.

What will happen to the results of the study?

We aim to publish the results of this research study. However, there will be no reference to any optometrist's survey results in any publication. A copy of the published research will be provided to you once the research study has been approved for publishing.

Who has reviewed the study?

The study has been reviewed by Aston University Research Ethics Committee and Parkway Independent Ethics Committee.

Researchers

Stacy Hsiao Lan Chan

Optometrist, Doctorate of Optometry student. Vision Sciences department, Aston University

Contact: [redacted]

Hannah Bartlett

Optometrist. Senior Lecturer. Vision Sciences department, Aston University.

Contact: [redacted]

Where can I get more information?

Please contact [redacted]) if you would like any more information about the study.

What if there is a problem?

If you have any concerns about anything to do with this study, you should speak to the research team and they will do their best to answer your concerns. You may contact either Stacy Chan at [redacted], or Hannah Bartlett at [redacted] or telephone [redacted]. If they cannot help you and you still have concerns or wish to make a complaint about the way in which the study has been conducted, then [redacted]

If you want an independent opinion of your rights as a research subject you may [redacted]).

Appendix K

Aston University

CONSENT FORM (PHASE 2)
Version 5: 31 October 2017

Project Title: Nutritional and smoking advice given to patients with or at risk of age-related macular degeneration (AMD) by optometrists in Singapore

Name of Researcher(s): Hannah Bartlett and Stacy Chan

		Initial
1	I confirm that I have read and understand the information sheet (Version 7 dated 31 October 2017) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.	
3	I agree to take part in the above study.	

Name of volunteer	Signature of volunteer	Date
Name of researcher	Signature of researcher	Date

Appendix L

Aston University
Life & Health Sciences

STUDY INFORMATION – Phase 2b

Version Two 29/04/2019

Nutritional and smoking advice given to patients with or at risk of age-related macular degeneration by optometrists in Singapore

Purpose of the study

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness registration in the developed world. In countries with an ageing population such as Singapore, the prevalence of AMD is expected to rise and following the AREDS 1 study, there were many nutritional supplements available in the market that claimed to preserve the vision of patients with AMD. However, patients or even some optometrists are unaware that the AREDS formulation is only beneficial for patients with moderate AMD. It is important for optometrists to know which patients meet the AREDS inclusion criteria, and could benefit from this specific formulation. Therefore, a clinical decision-making aid has been developed in the form of a flowchart to help optometrists choose the appropriate nutritional advice for their patients.

This study consists of two phases and this study information relates to Phase 2, where the aim is to validate this clinical decision-making aid.

Why is my child chosen to participate in this research study?

This study is open to any final year student optometrist who is currently pursuing his/her diploma in optometry in Singapore.

Does my child have to take part in this study?

No, your child's participation in this study is voluntary. Your child may decline to participate or to withdraw from participation at any time. You can allow your child to be in the study now and change your mind later without any penalty.

What does the study involve?

Your child will be requested to validate a clinical decision-making aid in the form of a flowchart by completing a self-efficacy survey before and after using the aid based on case scenarios. As part of the control for this study, he/she may be asked to read an article instead of using the clinical decision-making aid.

Firstly, your child will be presented with five AMD scenarios and asked to indicate the nutritional advice that he/she will provide for each case. After which, he/she will be requested to complete a short survey of seven questions that takes approximately five minutes and will assess his/her thoughts on giving nutritional advice to patients with or at risk of AMD. The survey will involve answering questions on a scale of 0 – 100.

Your child will then be provided with the clinical decision-making aid and be briefed on how to use it. Alternatively, he/she may be asked to read an article on AMD management. The five case scenarios will then be presented to your child again and he/she will be requested to provide the appropriate nutritional advice for each case with the aid or article. Finally, your child will be asked to complete the survey again with the seven questions that will take another five minutes of his/her time.

Will my child be compensated for his/her participation?

Your child will be reimbursed with S$10 coffee voucher for participation in this study.

Are there any risks or disadvantages of taking part in this study?

There are minimal potential risks in taking part in this study. Student optometrists may not be very confident in providing nutritional advice to AMD patients as they are not well versed in this area, or they could also be not seeing many AMD patients. However, their confidence may increase with the aid. There is a risk of breaching privacy and confidentiality in relation to your child's survey results but this risk will be minimised by keeping your child's data anonymous at all times. Ms. Stacy Chan will be responsible for putting your child's survey results onto a database and maintaining his/her privacy and confidentiality. Only Ms. Stacy Chan will have access to the database that is password protected.

What will happen to the results of the study?

We aim to publish the results of this research study. However, there will be no reference to any student optometrist's survey results in any publication.

Who has reviewed the study?

The study has been reviewed by Aston University Research Ethics Committee and Parkway Independent Ethics Committee.

Researchers

Stacy Hsiao Lan Chan

Optometrist, Doctorate of Optometry student. Vision Sciences department, Aston University

Contact: [redacted]

Hannah Bartlett

Optometrist. Senior Lecturer. Vision Sciences department, Aston University.

Contact: [redacted]

Where can I get more information?

Please contact [redacted]) if you would like any more information about the study.

What if there is a problem?

If you have any concerns about anything to do with this study, you should speak to the research team and they will do their best to answer your concerns. You may contact either Stacy Chan at [redacted], or Hannah Bartlett at [redacted] or telephone [redacted]. If they cannot help you and you still have concerns or wish to make a complaint about the way in which the study has been conducted, then you should contact the Aston University Director of Governance, [redacted]

Appendix M

Aston University
Life & Health Sciences

CONSENT FORM (PHASE 2b)

Version 2: 29 April 2019

Project Title: Nutritional and smoking advice given to patients with or at risk of age-related macular degeneration (AMD) by optometrists in Singapore

Name of Researcher(s): Hannah Bartlett and Stacy Chan

		Initial
1	I confirm that I have read and understand the information sheet (Version 2 dated 29 April 2019) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my child's participation in this study is voluntary and that he or she is free to withdraw at any time without giving any reason, without his or her legal rights being affected.	
3	I agree to allow my child to take part in the above study.	

_____	_____	_____
Name of child	Signature of child	Date
_____	_____	_____
Name of parent or Legal Guardian	Signature of parent or Legal Guardian	Date
_____	_____	_____
Name of researcher	Signature of researcher	Date