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The Economic Benefits of Using Lutein and Zeaxanthin Food Supplements in the European Union

Exploring the Burden of Age-related Macular Degeneration Attributed Vision Impairment and the Benefit of Lutein and Zeaxanthin Supplementation

Christopher Shanahan, M.S.

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ABSTRACT

This case study explores the possible health care cost savings that could be derived from the use of 10 mg of lutein and 2 mg of zeaxanthin by way of reducing the number of possible transitions from mild age-related macular degeneration (AMD) to the more costly and severe diagnosis of late stage AMD among Europeans age 50 and older. Specifically, this case study reviews the scientific literature in order to deduce the expected health benefits, in the form of a change in visual acuity (VA), that individuals can expect from the daily use of lutein and zeaxanthin food supplements. Key findings from this case study include:

- **Target Population**—over 17.1 million cases of AMD of any type were estimated in 2016 among adults age 50 and older in EU. It is expected that 2.53 million cases of AMD, or 18.9% of all AMD cases in Europe, are considered severe or late stage AMD. The total cost of managing the consequences of severe/late stage AMD in the EU is expected to be € 89.46 billion per year. This cost includes the direct costs of treating and managing the consequences of AMD and the indirect costs related to productivity loss. This translates to an annual health care cost of a severe/late stage AMD-attributed case transition in the EU of € 34,805 per transition.
- **Event Risk**—18.9% of AMD cases among adults age 50 and older in Europe will become severe, requiring costly direct and indirect medical treatments and care.
- **Methodology**—an assessment of various health state scenarios was analysed in order to determine the potential savings from avoided medical spending, or loss due to required medical spending, that is possible if one scenario occurred versus another. A review of the scientific literature related to lutein and zeaxanthin supplementation was undertaken and its possible effect on minimizing the number of cases of severe/late stage AMD as measured by the target population's average VA is provided. In order to compare differences in possible health states, changes in VA was used as a proxy to calculate the relative risk of suffering from severe AMD given the use and nonuse of a daily lutein and zeaxanthin regimen. Specifically, the benefits considered in this model are avoided expenditures related to severe/late stage AMD cases resulting from the use of a lutein and zeaxanthin food supplement. The result of these potential health care savings provides an economic indication of the monetary benefits the user of lutein and zeaxanthin can yield by reducing medical costs and enhancing quality of life.
- **Science-based Impact of Lutein and Zeaxanthin Use**—researchers studying the link between the use of lutein and zeaxanthin and a change in visual acuity among people with AMD found that those with mild/intermediate stage AMD using lutein and zeaxanthin supplements versus users of a placebo had a baseline LogMAR levels of VA by 0.04 basis points less than the placebo group (LogMAR = 0.5). The average baseline LogMAR level in the EU for the target population is estimated to be 0.574, or a 7.0% improvement in visual acuity. These findings overall imply that use of lutein and zeaxanthin could yield less mild to severe/late stage AMD case transitions compared to the placebo group
- **Economic Implications (Total EU)**
    - Total Avoidable AMD-attributed Transition Costs per year (S): € 6.20 billion
    - Net Avoidable AMD-attributed Transition Costs per year (B): € 4.97 billion
    - Net Avoidable AMD-attributed Transition Costs per person per year (B/Pop): € 291 per target person
    - Benefit/cost ratio (€ Avoided AMD-attributed Transition Costs per € 1 spent on Lutein and Zeaxanthin): € 5.01

PREFACE

In a perfect world, if adults aged 50 or older with no age-related macular degeneration (AMD) or with mild/intermediate AMD were to increase their daily lutein and zeaxanthin intake, the prevalence and progression of AMD would reduce, based on the overarching body of scientific evidence. Further, as approved therapies are only available for the severe form of the disease significant cost savings would result from the reduction of the incidence of advanced AMD.

The treatment costs of advanced AMD may vary in the future. Today, the primary direct burden of the treatment of AMD is limited to injections for the wet AMD. But new treatments for geographic atrophy (the advanced form of dry) are currently being investigated. New treatments of advanced wet AMD are also investigated. They may last longer and be effective, but they will also be costly. Specifically, as the incidence of AMD is expected to augment in the next decades because of the aging of the population, these new treatments will significantly increase the burden and the cost of AMD if the progression from mild to advanced stages is not reduced. There are also new biosimilar drugs in phase 3 trials that may help to contain or decrease costs when made available by 2020. Additionally, direct costs (procedures, follow-up visits) and indirect costs associated with loss of productivity from the patient suffering from the more severe stages or their caregivers need to be considered.

Some important challenges should be considered while reading the report:

1. The impact of indirect cost in productivity loss due to a patient with advanced AMD is debatable, as most of the patients are retired when it occurs (based of the current EU policies). Thus, the loss in productivity, and associated costs, are expected to be low when compared to other major cost contributions. This case study does, however, report that the indirect cost of AMD is representing approximately 25% of the total attributed health care costs. Thus, this difference ought to be considered when reviewing the aggregated results reported in this case study.
2. The case study looks at a subset of the population that has already developed early-stage AMD. The specific health benefits provided by lutein and zeaxanthin reviewed in this study is the slowing or avoidance of the progression of a more severe case of AMD among those individuals already diagnosed with mild AMD. Thus, the dietary intake of lutein and zeaxanthin does not mean that this micronutrition regimen would equally reduce the incidence of any type of AMD. Further research in the role of lutein and zeaxanthin in the primary prevention of AMD is underway.
3. The main challenge with supplementation is compliance. Nutritional supplementation means adopting a dietary routine. Health benefits of dietary supplementation are typically a long term, with gradual results rather than immediate effects, and the effectiveness of the regimen may be questioned by some patients. Consequently, the assumption of 100% compliance is not realistic. Unfortunately, the measurement of macular pigment optical density, which could provide an easy way of assessing compliance, is not yet standardized and not used in daily clinical practice currently.

Prof. Jean-François KOROBELNIK

Head of the Ophthalmology Department
University Hospital of Bordeaux, France
September 2017

THE HEALTH AND ECONOMIC BENEFITS OF LUTEIN AND ZEAXANTHIN FOOD SUPPLEMENTS

Introduction

Age-related macular degeneration (AMD) is an eye disease that affects the central part of the retina known as the macula.

Age-related macular degeneration (AMD) is a progressive degenerative eye disease and a major cause of vision loss among older Europeans. Age is a major risk factor for the development of AMD as the disease mostly inflicts people over the age of 50. Other risk factors include smoking, family history and genetics, and dietary and other lifestyle choices [2]. AMD is characterized by the degeneration of the central part of the retina known as the macula which is the area where the finest visual perception occurs [1, 2]. AMD is diagnosed by comprehensive eye examination to obtain images of the retina which enable to detect the presence, number and dimension of *drusen (*yellow deposits beneath the retina that represent the hallmark of AMD), and the eventual presence of newly formed and/or leaking blood vessels. Visual acuity is always assessed to verify how the disease affects visual function [2]. AMD, which inhibits the ability to see objects directly ahead, can cause irreversible and progressive decline in an individual's independence and ability to perform daily activities, which often leads to significant emotional distress and significantly impacts quality of life [2]. There are three stages of AMD – early ("dry" AMD), intermediate ("dry AMD") and late or advanced AMD (which can be in either the "dry" form (Geographic Atrophy) or the "wet" form which is accompanied by choroidal neovascularisation) and people move from one stage to the other as the disease progresses [5]. However, in some people AMD progresses slowly for a long time and can even go unnoticed before it is too late while in other the disease can progress faster [1, 2].

Early AMD is characterised by the presence of abnormalities in the retinal pigment epithelium and the presence of small or medium-sized drusen. As the disease progresses to an intermediate stage drusen increase in number and size ("large drusen"). The presence of a large drusen represents a strong indicator of increased risk for the subject to progress to advanced AMD [1, 5]. Early stage AMD, which accounts for large majority of diagnosed cases in the European Union, does not usually cause significant vision loss [3]. If left unattended, however, early stage AMD transitions into more severe cases of intermediate to advanced AMD, which are associated with significant vision loss and a reduction in the quality of life [2, 3]. One form of advanced AMD is geographic atrophy, which typically progresses slowly and generally affects the central vision over the course of many years. Some people will only have one eye affected by dry AMD and thus will have no noticeable change in visual acuity; but if both eyes are affected, then there will be a significant reduction in visual acuity and consequently increased disability [1].

AMD can impair an individual's independence and ability to perform daily activities, which often leads to significant emotional distress and significantly impacts quality of life.

Wet, or neovascular, AMD occurs when irregular blood vessels begin to form underneath the macula and over time begin to leak fluid, which cause swelling and damage to the macula and therefore impact central, straightforward vision. Wet AMD is the more aggressive, or severe, form of advanced AMD [2]. There are some approved drug therapies targeting advanced AMD, such as anti-vascular endothelial growth factor (VEGF) drug injections, though options are limited and significant in cost (thousands of euros) and require monthly revisit to the ophthalmologist office for additional treatments [2]. Late stage AMD accounts for approximately 4.7% of the total prevalence of AMD in the European Union according to a recent meta-analysis conducted by Wong et. al. in 2014 [3].

As discussed, visual acuity (VA) is assessed in AMD patients in order to measure the relative severity of a given case of AMD. There are many validated charts used in clinical settings to measure VA such as the LogMAR (**Log**arithm of the **M**inimum **A**ngle of **R**esolution) chart [7, 8]. LogMAR is commonly used in eye disease related statistical analyses because it provides an easy way to equate a change in the resolution of text (or line on a LogMAR chart) to a fixed change in VA [5]. A LogMAR score of 0.0 indicates perfect vision (corresponding to 6/6 on the metre visual acuity scale or 20/20 on the U.S. scale); a LogMAR score of 0.5 indicates the baseline level of low vision disability (equal to 6/18 on the metre visual acuity scale or 20/63 on the US scale); and a LogMAR score of 1.0 indicates baseline severe visual impairment (equal to 6/60 on the metre visual acuity scale or 20/200 on the US scale) [7, 8].

The degree of disability varies by severity of AMD. Early AMD is generally associated with near normal vision or moderate vision loss. Moderate vision loss is characterized as having some vision problems that makes it difficult for patients to recognise faces or objects across a room [2, 3]. WHO defines "moderate visual impairment" as visual acuity >0.5 LogMAR (6/18 on the metre visual acuity scale or 20/63 on the U.S. scale), and "severe visual impairment" at visual acuity <1.0 LogMAR (6/60 on the metre visual acuity scale or 20/200 on the U.S. scale) [8]. The more severe late stage AMD is characterised by a significant reduction in visual acuity which causes difficulty in daily activities, some emotional impact (for example worry), and some difficulty going outside the home without assistance thus requiring long-term professional care [2, 3, 5, 6, 8].

For the purposes of this study and taking a conservative approach, the 0.5 LogMAR benchmark is assumed to represent the visual acuity of a typical person with early and intermediate AMD, since this LogMAR level is typically associated with minimal vision disability. It should be noted that the level of disability associated with this LogMAR value will vary from person to person due to how AMD progresses (e.g.: one eye or both eyes). A 1.0 LogMAR benchmark is used to represent the visual acuity of a typical person with Late AMD. since a LogMar of 1.0 and above is typically associated with severe vision disability. It should be noted that this LogMAR value for Late AMD will vary from person to person due to how AMD progresses (e.g.: one eye or both eyes).

Age-related macular disease is a difficult condition to track in terms of number of hopitalisations. Currently, AMD is categorized by the World Health Organization in the "other" eye disease category (ICD-10 code H55-H59) and further data segmentation is not available. However, WHO tracks the burden of AMD through its Global Health Observatory (GHO) database in terms of expected prevalence and overall quality of life among those suffering from AMD [7]. WHO is able to do this because WHO experts track a metric called a disability-adjusted life year, or DALY, by disease condition and by country. The premise behind a DALY is that an individual's quality of life correlates with earning potential. A healthy person is able to enjoy life, be more productive, and contribute more to society than a sick person who is in pain, immobile, or physically or mentally limited. Specifically, the concept of disability-adjusted life year (DALY) is based on the idea that the onset of disease can negatively impact a person's quality of life and personal productivity [10].[1]

1 In order to determine an individual's total disability-adjusted life years lost due to a given disease remaining life, one must determine the difference between an individuals expected age of death had the individual stayed healthy and their current age, then subtract out all years expected to be lost due to premature death and then the remaining life years are further "discounted for disability" caused by an individual suffering from a specific disease condition [10].
DALY can be expressed as DALY = YLL+ YLD, where YLL is the total number of years lost life or total number of deaths caused by the disease (N) multiplied by the life expectancy (L), or YLL = N x L, and YLD is the total number of years lost to disability [10]. YLD is the product of the number of disease cases incidents (I), the duration of case until remission or death (L), and a disability weight (DW) [10]. If DW = 0, then the individual is considered in optimal health during the entire year. If DW = 1, then the individual is deceased over the entire year. The continuum between 0 and 1 reflects the transition from optimal health to increasingly worse health leading to death for some or all of the year [10]. Disability weights are somewhat comparable across diseases, but are even more important when understanding the severity of disability due to a specific disease like AMD. Alternatively, YLD can be estimated by taking the product of the number of prevalent cases and the disability weight [10]. The GHO database reports the estimated number of prevalent cases per country and disability weights, both of which was used in this case study's analysis.

17 million people have AMD of any type in the European Union which accounts for 31.5% of all cases of AMD globally.

The degree of disability varies by severity or disease stage where the expected disability weight assigned to those with early stage, or mild, AMD is a 0.03 per year reduction in remaining life years. This is reflective of the marginal disability caused by the limited discomfort, pain, or distress caused by vision problems associated with early AMD (LogMAR <0.5) and the consequential restrictions in mobility. The disability weight increases significantly to a 0.18 per year reduction in remaining life years for those suffering from late stage, or severe, AMD which is associated with severe vision loss (LogMAR ≥ 1.0) and causes significant difficulty in performing daily activities, some emotional distress, and some difficulty moving around without assistance. For a given country, a higher average disability weight can serve as a proxy for severe case prevalence relative to mild cases of AMD which in turn can be used to derive relative prevalence of severe versus mild AMD.

Also, multiple studies have reported on the prevalence of age-related macular degeneration globally and in Europe specifically [2, 3, 4, 5, 6, 7]. According to results of the systematic review of 14 population-based studies conducted by Colijn et al., and published in the journal Ophthalmology in 2017, 30 to 50 million people suffer from any type of AMD globally [4]. In Europe, the prevalence of AMD is also significant. Conservatively, Europe accounts for 31.5%[2] of global cases of AMD of any type according to Wong et al. (2014). According to Colijn et al. (2017) and author analysis, the mean EU projected number of people with any stage AMD in 2016 is expected to be more than 17 million people[3] and is expected to rise more than 30% by 2040. Furthermore, an estimated 2.52 million people suffered from late stage AMD in Europe in 2016 [4]. This suggests that over 14 million people in Europe suffer from early and intermediate AMD and are at risk of transitioning to a severe diagnosis if left unaddressed. Colijn et al does not provide per EU-country AMD prevalence but the authors do provide prevalence by major regions within the EU [4]. In order to estimate prevalence of AMD for each country, total EU population shares per country were used. Table 1 shows the current prevalence of age-related eye disease by severity and by EU country derived from the findings of Colijn et al. (2017) [4].

2 This figure is from Supplement Table 7 from Wong et al. 2014 [3].
3 This figure is based on an analysis of the results of the Colijn et al. 2017 meta analysis [4]

Table 1
Burden of Age-related Macular Degeneration: Population Descriptive Statistics

Country	Total Population, age 50 and older	Population with AMD, age 50 and older[4]	% of Population with AMD, age 50 and older per country[6]
Austria	3,397,820	266,155	7.8%
Belgium	4,332,158	342,666	7.9%
Bulgaria	2,940,205	232,508	7.9%
Croatia	1,705,602	141,769	8.3%
Cyprus	280,794	21,602	7.7%
Czech Republic	3,989,353	323,145	8.1%
Denmark	2,180,170	173,741	8.0%
Estonia	509,270	40,272	7.9%
Finland	2,238,822	187,412	8.4%
France	25,435,541	2,051,812	8.1%
Germany	35,499,895	2,853,838	8.0%
Greece	4,388,985	347,075	7.9%
Hungary	3,765,076	307,796	8.2%
Ireland	1,422,141	104,023	7.3%
Italy	25,904,190	2,572,585	9.9%
Latvia	793,490	68,057	8.6%
Lithuania	1,158,312	99,465	8.6%
Luxembourg	193,043	14,193	7.4%
Malta	169,852	15,105	8.9%
Netherlands	6,587,899	524,083	8.0%
Portugal	4,250,287	416,290	9.8%
Poland	13,933,966	1,064,077	7.6%
Romania	7,172,994	578,778	8.1%
Slovakia	1,893,762	136,622	7.2%
Slovenia	827,739	67,076	8.1%
Spain	17,788,752	1,707,589	9.6%
Sweden	3,733,535	328,502	8.8%
United Kingdom	23,799,250	2,082,825	8.8%
Total EU	200,292,902	17,069,061	8.5%

Source: Eurostat. Global Health Data Exchange. Institute for Health Metrics and Evaluation. University of Washington and Frost & Sullivan analysis

8.5% of European adults age 50 and older are diagnosed with AMD, a degenerative eye disease characterised by a progressive reduction in visual acuity (VA), leading to irreversible blindness in severe cases.

[4] For the purposes of this study, the number of people with AMD per country is the same proportion as the total population due to lack of per country prevalence estimates.

Table 1 (continued)
Burden of Age-related Macular Degeneration: Population Descriptive Statistics

Country	Population with Mild/Early Stage AMD, age 50 and older	Population with Severe /Late Stage AMD, age 50 and older	% of Target Population with Mild/Early Stage AMD	% of Target Population with Severe/Late Stage AMD
Austria	227,289	38,867	85.4%	14.6%
Belgium	292,867	49,799	85.5%	14.5%
Bulgaria	200,097	32,411	86.1%	13.9%
Croatia	121,808	19,961	85.9%	14.1%
Cyprus	18,655	2,947	86.4%	13.6%
Czech Republic	278,396	44,748	86.2%	13.8%
Denmark	141,758	31,984	81.6%	18.4%
Estonia	34,659	5,614	86.1%	13.9%
Finland	152,501	34,911	81.4%	18.6%
France	1,747,046	304,766	85.1%	14.9%
Germany	2,440,082	413,755	85.5%	14.5%
Greece	298,694	48,382	86.1%	13.9%
Hungary	264,689	43,106	86.0%	14.0%
Ireland	85,117	18,906	81.8%	18.2%
Italy	2,241,522	331,063	87.1%	12.9%
Latvia	58,141	9,916	85.4%	14.6%
Lithuania	84,660	14,806	85.1%	14.9%
Luxembourg	12,183	2,010	85.8%	14.2%
Malta	13,538	1,567	89.6%	10.4%
Netherlands	428,149	95,934	81.7%	18.3%
Portugal	362,742	53,548	87.1%	12.9%
Poland	915,574	148,503	86.0%	14.0%
Romania	499,095	79,683	86.2%	13.8%
Slovakia	118,429	18,192	86.7%	13.3%
Slovenia	57,501	9,574	85.7%	14.3%
Spain	1,487,699	219,891	87.1%	12.9%
Sweden	267,361	61,141	81.4%	18.6%
United Kingdom	1,688,853	393,972	81.1%	18.9%
Total EU	14,539,105	2,529,956	81.1%	18.9%

Source: Eurostat. Global Health Data Exchange. Institute for Health Metrics and Evaluation. University of Washington and Frost & Sullivan analysis

The burden of AMD has significant economic consequences. BrightFocus Foundation states that the global total cost of AMD is expected to be $343 billion per year, of which $255 billion (74.3%) is contributed to direct health care costs [11]. According to Wong et. al (2014), 31.5% of global AMD cases were bore by Europeans [3] and it was expected that the proportion of global costs distributed regionally is highly correlated to AMD prevalence. Thus, the expected unadjusted total costs of AMD in Europe are approximately 31.5% of global costs, or $108.04 billion in total costs. Converting this to euros at a €0.95 to $1 ratio yields €102.64 billion.

To reflect the variance in the cost of living and purchasing power across each of the EU countries, the PPP ratio weights (Belgium € = 100) was applied to the European average to calculate certainty equivalent cost of AMD treatment per person per country as shown in Table 2 [32]. The certainty equivalent cost of AMD treatment per person per country can then be multiplied by the total number of people with AMD per country to provide a PPP-adjusted total cost of AMD per country. In addition, certainty equivalent cost of AMD treatment per person per country can also be divided by the proportion of people with severe/late stage AMD relative to the total target population of individuals age 50 and over with any type of AMD (4.7%) to determine the estimated cost of AMD treatment per case or transition. The total PPP-adjusted health care costs associated with severe/late stage AMD in the EU is estimated to be €89.46 billion in 2016 among all adults age 50 and older [3, 5, 11, 32].

Based on the above assessment, it is expected that the PPP-adjusted annual cost of managing severe/late stage AMD in the EU, adjusted for the excluded cost of lutein and zeaxanthin and defined as variable *h*, is €34,805 per transition in 2016. This cost excludes the annual cost of lutein and zeaxanthin in order to avoid double counting. A significant portion of this cost is related to severe/late stage AMD cases and is tied to post-diagnosis anti-VEGF drug treatments, laser-enabled therapies and surgeries, long-term home/nursing care services and outpatient visits [11]. See Table 2, and Charts 1 and 2 for the total economic burden of AMD per country and the average annual cost of AMD per case by EU country. Yes

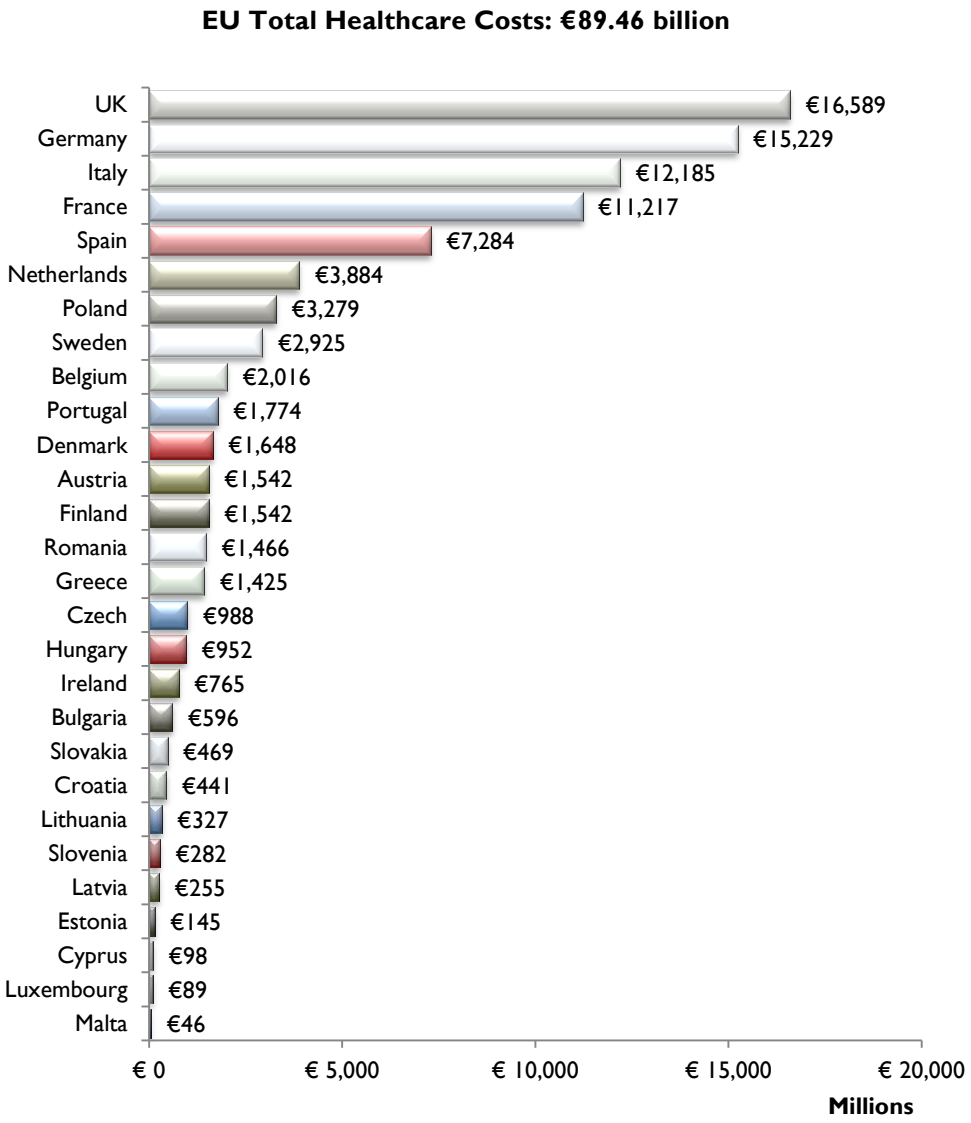
The average cost of managing AMD in the EU was €34,805 per case and the total health care cost of AMD in the EU was estimated at €89.46 billion in 2016.

Table 2
Total Burden of Age-Related Eye Disease: AMD-attributed Event Costs

Country	PPP-adjusted Annual Cost of AMD per EU Country	h: Estimated PPP-adjusted Cost of AMD per transition per EU Country
Austria	€1,542,101,645	€39,677
Belgium	€2,016,192,053	€40,487
Bulgaria	€596,461,949	€18,403
Croatia	€440,800,355	€22,084
Cyprus	€97,619,873	€33,125
Czech Republic	€988,202,079	€22,084
Denmark	€1,648,073,343	€51,528
Estonia	€144,637,700	€25,764
Finland	€1,541,921,848	€44,167
France	€11,217,203,080	€36,806
Germany	€15,228,676,573	€36,806
Greece	€1,424,587,801	€29,445
Hungary	€951,938,388	€22,084
Ireland	€765,436,594	€40,487
Italy	€12,185,110,891	€36,806
Latvia	€255,486,671	€25,764
Lithuania	€326,959,133	€22,084
Luxembourg	€88,784,072	€44,167
Malta	€46,127,138	€29,445
Netherlands	€3,884,037,762	€40,487
Portugal	€1,773,785,874	€33,125
Poland	€3,279,478,968	€22,084
Romania	€1,466,403,569	€18,403
Slovakia	€468,706,698	€25,764
Slovenia	€281,913,833	€29,445
Spain	€7,283,957,530	€33,125
Sweden	€2,925,466,662	€47,848
United Kingdom	€16,588,603,586	€42,106
Total EU	€89,458,675,671	€34,805

Source: Deloitte Access Economics, BrightFocus Foundation, and Frost & Sullivan analysis

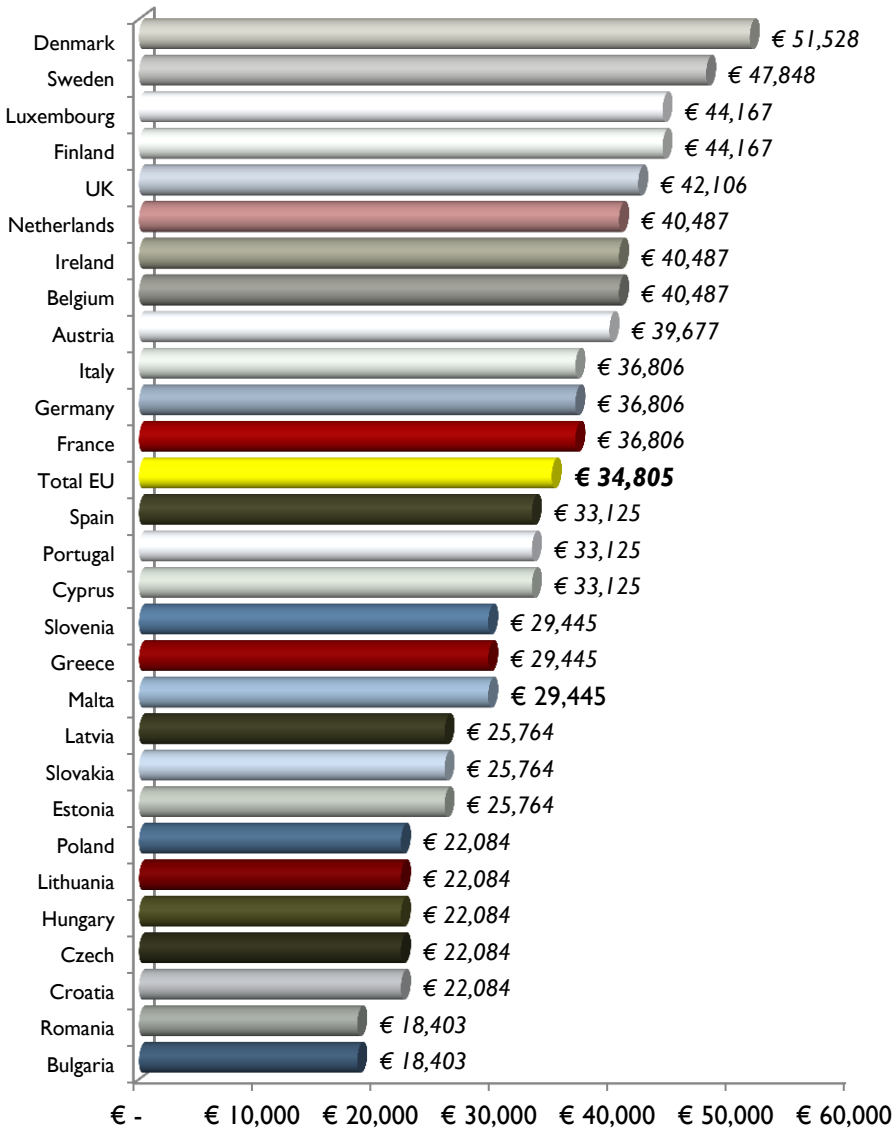
Chart 1
PPP-Adjusted Total Annual Health Care Cost of Severe Cases of AMD per EU Country, € million, 2016



Source: Deloitte Access Economics, BrightFocus Foundation, and Frost & Sullivan analysis

Chart 2
Estimated Monetary Cost of a Severe AMD-attributed Case per EU Country,
€/Case, 2016

EU Average: €34,805 per Case



Source: Deloitte Access Economics, BrightFocus Foundation, and Frost & Sullivan analysis

The Benefits of Lutein and Zeaxanthin

Lutein and zeaxanthin are xanthophylls, carotenoids that are typically found in the human diet. Rich sources of lutein and zeaxanthin are green vegetables, particularly dark green leafy vegetable such as spinach and kale, orange pepper, maize and eggs [12, 13]. Lutein and zeaxanthin are well known for their antioxidant properties that help protect cells against damage caused by dangerous, naturally occurring chemicals known as free radicals. Also, lutein and zeaxanthin are selectively concentrated in the macula lutea, where they are a key component of the macular pigment, which suggests their important role in protecting eyes and eyesight [12, 13, and 14]. Specifically, recent evidence has found that lutein and zeaxanthin are believed to play roles in protecting the eye from oxidative damage caused by light interacting with other pigments in the retina [12, 13, and 14]. Similar to all the carotenoids lutein and zeaxanthin are not synthesized by the body; these nutrients must be consumed from the diet from lutein and zeaxanthin rich foods or through food supplementation [12]. In the European Union, there is no EFSA-recognized recommended daily intake level for lutein and zeaxanthin, but the American Optometric Association (AOA) proposes that 10 mg per day of lutein and 2 mg per day of zeaxanthin benefits eye health based on results of recent clinical research [14]. This recommended dose, which is based on the observations from the US National Eye Institute sponsored Age-Related Eye Disease Study II (AREDS2), is assumed to be sufficient to derive the expected benefits explored in this economic analysis and is also the quantity found in the majority of products currently in the market in US and Europe, [15, 16].

Overall, the state of the science of the AMD-related health benefits from using lutein and zeaxanthin is substantial. There are over 20 years of scientific publications indicating that higher lutein and zeaxanthin intake is associated with a higher density of the macular pigment (MP) and exploring the beneficial role of lutein and zeaxanthin supplementation for eye health. However, the heterogeneity of research design, sample population definitions, tested end points adopted by researchers in the field has made it difficult to compare and aggregate the findings of this body of literature. Specifically, it should be noted that all the epidemiological studies described below explore the effect of lutein intake in reducing the risk of AMD. Moreover, since it is almost impossible to conduct an intervention study to demonstrate the cause effect relationship between lutein and zeaxanthin and the reduction of risk of AMD (and although MP has been found to be lower in subject suffering from AMD compared to healthy subjects, its role as potential biomarker for AMD has not yet been officially established) almost all the intervention studies looked at the effect of supplementation on relative visual function given the presence of AMD or reduced progression of AMD from mild to severe cases.

AMD patients who use lutein and zeaxanthin supplements witnessed less transitions to severe cases of AMD compared to a placebo group, implying that the group of lutein and zeaxanthin users would also bear less disease management costs.

The overarching evidence points to a link between lutein and zeaxanthin intake and AMD-attributed health benefits. One example of a study that directly tested a link between AMD event risk and lutein and zeaxanthin intake is SanGiovanni et al., (2007) which was a case-controlled study of 4,519 subjects in the U.S., most of whom had some degree of AMD [17]. Data on dietary intake were analysed and tested versus AMD incidence. A statistically significant reduction in neovascular AMD incidence (odds ratio 0.65; 95% CI 0.45 to 0.93) was identified in comparing the highest and lowest quintiles of lutein and zeaxanthin intake [17].

Tan et al., (2008) conducted a population-controlled cohort study of diet and AMD incidence in 3,654 Australians [18]. Participants in the highest tertile of dietary lutein and zeaxanthin intake had a relative risk for incident AMD of 0.35 (95% CI 0.13 to 0.92) [18]. Another study that looked at the link between lutein and zeaxanthin intake and AMD risk was Seddon et al., (2010) which compared 545 subjects with AMD to 275 subjects without AMD in a case-controlled study [19]. Higher lutein intake (highest tertile) was associated with a reduction in risk of advanced AMD (OR 0.6 (95% CI 0.4 to 1.0)) when compared to lower intake (first tertile) [19]. These results add on the findings published by the same lead author in 1994 that showed for the first time that a higher dietary intake of lutein and zeaxanthin was associated with a reduction in risk of advanced neovascular AMD (OR 0.43 (95%CI 0.2 to 0.7) for higher quintile versus lower quintile of intake [20].

The largest intervention study conducted to date is AREDS2, a randomised, double-blind, placebo-controlled trial (RCT) with 4,203 subjects at risk for progression to advanced AMD [16]. In this study, the subjects took a daily regimen of lutein (10 mg) and zeaxanthin (2 mg), omega-3 fatty acids, lutein/zeaxanthin + Omega 3 in combination or placebo in addition to the original AREDS formula (high quantity of vitamin C, vitamin E, beta-carotene, zinc and copper) and eye examinations were conducted over a median of 5 years to assess progression to advanced AMD [16]. The primary analysis compared subjects supplemented with the AREDS formulation and lutein plus zeaxanthin to those supplemented with AREDS formulation only. The hazard ratio for progression to advanced AMD was 0.90 for the lutein plus zeaxanthin group (98.7% CI 0.76 to 1.07). However the main analysis in AREDS2 comparing all subjects taking lutein and zeaxanthin with all subjects not taking these carotenoids showed that lutein and zeaxanthin intake resulted in a 10% reduction of progression to advanced AMD (HR 0.90; 95% CI 0.82-0.99; p=0.04) [16].

Recent studies have revealed that supplementation with lutein and/or zeaxanthin in AMD patients leads to an increase in macular pigment and improved visual acuity [21, 22, 23, 24, 25, 26, 27, 28, 29, and 30]. Liu et al. conducted a detailed meta-analysis of eight RCTs of AMD patients (n=1,176 patients not presenting advanced AMD) that explored the relationship between lutein and zeaxanthin supplementation and its effect on visual acuity [21]. The intervention lasted from 6 to 36 months and the quantity of lutein and zeaxanthin administered ranged from 6 to 20mg for lutein and 0 to 10mg for zeaxanthin. The researchers found that the groups of AMD subjects supplemented with >10mg of lutein and/or zeaxanthin[5] –had a significant decrease in LogMAR level of VA by 0.04 basis points compared to subjects taking placebo and each 1mg/day increase in intake of these carotenoids was related to a 0.003 LogMAR reduction. Additional benefits were observed in complementary measures of visual function such as contrast sensitivity [21]. Correlation analysis indicated that improvement in VA was associated with an increase in macular pigment optical density (MPOD) induced by lutein and zeaxanthin supplementation, which is an indication that the enrichment of macular pigment might be responsible for the observed functional improvements. The observed improvements in visual acuity resulting from lutein and zeaxanthin supplementation suggest a protection against the deterioration of visual function which characterises this progressive degenerative eye condition. Furthermore, it is important to note that the intake of lutein and zeaxanthin from the diet in the EU is well below the levels of intake observed to be beneficial for eye health. The study from O'Neill 2001 assessing carotenoid intakes in 5 EU countries indicated average intake of only 2.18 mg (range 1.56-3.2) from the diet [30].

5 The recognised AREDS2 formulation is 10mg of lutein and 2mg of zeaxanthin per day which is the standard amount used for the purposes of this case study. This is the formulation used by the leading companies in EU although some of them use higher amount of lutein and lower amounts of zeaxanthin.

Methods

This case study explores the possible direct economic benefit that could be expected from the use of lutein and zeaxanthin food supplementation as a means to help reduce the number of AMD cases that transition from the more manageable and less debilitating early/intermediate dry AMD to more severe, and costly, advanced AMD among those individuals in the EU with non-advanced AMD. One proxy of severity of AMD is the degree of visual acuity (VA) which is a common method of measuring the effectiveness of an AMD case-reducing regimen as demonstrated by Liu et. al 2014 [21]. It should be noted that "severity" of AMD is highly dependent on a given patient's perception and tolerance, which is why the authors of this study looked at the relatively more objective measure of visual acuity which can be assessed in an ophthalmic examination. Specifically, a review of the scientific literature related to lutein and zeaxanthin supplementation and its possible effect on minimizing the number of cases of severe/late stage AMD as measured by the target population's average VA is provided. Furthermore, this case study deduces the expected health benefits of people age 50 and older with AMD using lutein and zeaxanthin food supplements and provides the expected economic benefit equivalent for EU-based health care payer decision makers.

The health economic analysis presented in this case study is based on an assessment of various health state scenarios and determining the potential savings, or loss, that are achieved if one scenario of events occurred versus another [31, 33]. The benefits considered in this model are avoided medical expenditures related to severe/late stage AMD cases resulting from the use of a lutein and zeaxanthin food supplement. The result of these potential healthcare savings provides an economic indication of the monetary benefits the user of lutein and zeaxanthin can yield for all of society through medical cost reduction and increased productivity. Table 3 provides a list of the key variables used to conduct this health economic analysis.

Table 3
List of Key Variables used in this Economic Analysis

A	Number of possible avoided AMD case transitions from mild/intermediate to severe condition if everybody in a specified target population used lutein and zeaxanthin
B	Total potential net economic benefits yet to be realised from use of a lutein and zeaxanthin food supplement daily
S/Pop	Benefit per User
C	Total cost of a lutein and zeaxanthin regimen
d	The expected per person cost of lutein and zeaxanthin utilisation per year
h	The expected cost of a severe/late stage AMD case-attributed medical event
Pop	Target Population
S	Total potential savings from reduced hospital service utilisation following severe/late stage AMD case transitions that are realisable if the entire target population were to sufficiently utilise a lutein and zeaxanthin food supplement
S/C	Benefit Cost Ratio
x	Share of Population with Mild/Intermediate AMD
y	Share of Population with Severe AMD

Source: Frost & Sullivan analysis

Users with mild AMD of 10 mg of lutein and 2 mg of zeaxanthin – typically in an AREDS2 formulation – versus users of a placebo had a baseline LogMAR level of VA by 0.04 basis points less than the placebo group.

In order to determine the percent change in the number of costly severe/late stage AMD cases given use of lutein and zeaxanthin (scenario 1) versus non-use (scenario 2), we first recall from Table 1 the current prevalence of mild/intermediate stage and severe/late stage AMD in each EU country of investigation. 81.1% of AMD cases are mild/intermediate stage which is associated with an average LogMAR baseline level of 0.50 and the rest of the cases (18.9%) are severe AMD stage which is associated with an average LogMAR baseline level of 1.00, [3, 7]. The weighted average LogMAR baseline level for the total EU population can easily be found by calculating the sum-product of the typical LogMAR baseline levels for mild/intermediate stage and severe and the current prevalence of mild and severe/late stage AMD. Thus, the weighted average equation is 0.5*81.1% + 1.0*18.9%, which equals an average LogMAR of 0.574.[6] It is expected that any regimen, including the use of a lutein and zeaxanthin food supplement, that reduces the average LogMAR baseline level through the change in the share of the population will indicate the efficacy of the regimen in question.

Applying the findings of Liu et al. 2014 (0.04 change in LogMAR given the use of lutein and zeaxanthin) and calculating the updated share of population of AMD cases given use of lutein and zeaxanthin provides the change in severe/late stage AMD cases needed to calculate the number of costly AMD transitions avoided [21]. Based on this finding, the groups of users of lutein and zeaxanthin versus users of a placebo had a baseline LogMAR level of VA by 0.04 basis points less than the placebo group. Thus, the difference in average LogMAR baseline levels for the total EU and the updated LogMAR baseline level given use of lutein and zeaxanthin is 0.534 (the difference between 0.574 and 0.04) corresponding to 7.0% reduction in the absolute risk of a severe AMD case transition. It should be noted that the 7.0% reduction in risk obtained with this approach is supported by the findings of the AREDS2 study which indicated a 10% reduction of progression to advanced AMD with the use of 10mg of lutein and 2 mg of zeaxanthin [16].

Table 4 provides the share of AMD cases by severity, the associated average LogMAR baseline level for each EU country and the % decrease in baseline LogMAR given the use of lutein and zeaxanthin.

6 Let x be the share of the population with mild/intermediate stage AMD with VA of 0.50 and let y be the share of the population with severe/late stage AMD with a VA of 1.00. There are two groups of AMD severity – mild/intermediate AMD and severe AMD – thus, x + y = 100%. The equation used to determine the average LogMAR baseline level given use of lutein and zeaxanthin is 0.50*x + 1.00*y = z. Substituting y for 1-x in the proceeding equation gives the updated equation 0.50*(1-y) + (y) = z.

Table 4
Burden of Age-related Macular Degeneration and Anticipated Benefits of Lutein and Zeaxanthin: Baseline LogMAR per Country and Hypothetical LogMAR per Country given use of a Lutein and Zeaxanthin Food Supplement

Country	Baseline LogMAR per Country	Hypothetical LogMAR per Country Given use of L&Z	% Decrease in Baseline LogMAR given use of L&Z
Austria	0.573	0.533	6.98%
Belgium	0.573	0.533	6.98%
Bulgaria	0.570	0.530	7.02%
Croatia	0.570	0.530	7.01%
Cyprus	0.568	0.528	7.04%
Czech Republic	0.569	0.529	7.03%
Denmark	0.592	0.552	6.76%
Estonia	0.570	0.530	7.02%
Finland	0.593	0.553	6.74%
France	0.574	0.534	6.97%
Germany	0.572	0.532	6.99%
Greece	0.570	0.530	7.02%
Hungary	0.570	0.530	7.02%
Ireland	0.591	0.551	6.77%
Italy	0.564	0.524	7.09%
Latvia	0.573	0.533	6.98%
Lithuania	0.574	0.534	6.96%
Luxembourg	0.571	0.531	7.01%
Malta	0.552	0.512	7.25%
Netherlands	0.592	0.552	6.76%
Portugal	0.564	0.524	7.09%
Poland	0.570	0.530	7.02%
Romania	0.569	0.529	7.03%
Slovakia	0.567	0.527	7.06%
Slovenia	0.571	0.531	7.00%
Spain	0.564	0.524	7.09%
Sweden	0.593	0.553	6.74%
United Kingdom	0.595	0.555	6.73%
Total EU	0.574	0.534	6.97%

Source: Global Health Data Exchange, Wong et al. 2014, and Frost & Sullivan analysis

The average LogMAR baseline level for the total EU population, which is the sum-product of the typical LogMAR baseline levels for mild and severe and the current prevalence of mild and severe AMD, is 0.574.

The anticipated change in the average LogMAR baseline level given use of lutein and zeaxanthin among all adults age 50 and older with AMD implies that the distribution of cases between the mild and severe categories of AMD will also change. Applying a simple algebraic equation will yield the hypothetic share of population of mild and severe/late stage AMD cases given the 100% utilisation of a lutein and zeaxanthin food supplement as shown in Table 5 and the logical steps below. Table 5 provides the calculation details used to determine the number of severe case transitions that could be avoided is the total population of adults age 50 and older with AMD used a lutein and zeaxanthin food supplement.

Table 5
Benefits of Lutein and Zeaxanthin: Calculation Steps for determining the % Change in Number of Costly Severe AMD cases given use of Lutein and Zeaxanthin Supplements, Total EU, 2016

Step	Measure	Mild AMD	Severe AMD	Average AMD	Notes
A	**Share of Population of AMD cases**	81.1%	18.9%	--	Source: Global Health Data Exchange, Wong et al. 2014, and Frost & Sullivan analysis
B	**LogMAR Baseline Level**	0.50	1.00	0.574	The average LogMAR baseline level is the sum product of the typical LogMAR baseline levels for mild and severe and the current prevalence of Mild and Severe AMD
C	**Change in LogMAR given use of lutein and zeaxanthin**	--	--	-0.04	Source: Liu et al. 2014
D	**Updated LogMAR Baseline Level given use of lutein and zeaxanthin**	0.50	1.00	B – C = 0.534 (6.97% reduction in transitions)	The difference in average LogMAR baseline level and the updated LogMAR baseline level given use of lutein and zeaxanthin
E	**Updated Share of Population of AMD cases given use of lutein and zeaxanthin**	82.4% (The difference in prevalence (1.3%) remains in the mild case portion of the population)	17.6% (6.97% reduction in case transitions – 18.9%*(1-6.97%))	--	Calculated given the use of lutein and zeaxanthin

Source: Frost & Sullivan analysis

Thus, if the total population of adults age 50 and older with AMD in the EU used a lutein and zeaxanthin food supplement, then the change in the number of costly cases of severe/late stage AMD, as measured by the average VA of the total population of AMD cases, will decrease by 6.97% (relative risk reduction). In terms of avoided AMD transitions from mild to severe out of the total number of 17.1 million cases in the EU, 175,889 case transitions could be avoided is the total target population used a lutein and zeaxanthin food supplement. Table 6 provides the calculated results of the number of severe/late stage AMD case transitions avoided from use of a lutein and zeaxanthin food supplement for the target population.

Table 6
Benefits of Lutein and Zeaxanthin: The Anticipated Number of Severe AMD Case Transitions that could be avoided from use of a Lutein and Zeaxanthin Food Supplement per year, Adults age 50 and older with AMD, 2016

Country	% of Target Population with Mild AMD Given Use of L&Z	% of Target Population with Severe AMD Given Use of L&Z[7]	Population with Severe AMD, age 50 and older, Given Use of L&Z	Population with Mild AMD, age 50 and older, Given Use of L&Z	A: Avoided Case Transitions	%A: Avoided Case Transitions as a Per cent of total EU
Austria	86.42%	13.58%	36,153	230,002	2,713	1.54%
Belgium	86.48%	13.52%	46,321	296,346	3,478	1.98%
Bulgaria	87.04%	12.96%	30,135	202,372	2,276	1.29%
Croatia	86.91%	13.09%	18,561	123,208	1,400	0.80%
Cyprus	87.32%	12.68%	2,740	18,862	207	0.12%
Czech Republic	87.13%	12.87%	41,604	281,541	3,144	1.79%
Denmark	82.83%	17.17%	29,823	143,918	2,161	1.23%
Estonia	87.04%	12.96%	5,220	35,053	394	0.22%
Finland	82.63%	17.37%	32,557	154,856	2,354	1.34%
France	86.18%	13.82%	283,538	1,768,274	21,228	12.07%
Germany	86.51%	13.49%	384,846	2,468,991	28,909	16.44%
Greece	87.04%	12.96%	44,985	302,091	3,397	1.93%
Hungary	86.98%	13.02%	40,081	267,714	3,025	1.72%
Ireland	83.06%	16.94%	17,626	86,397	1,280	0.73%
Italy	88.04%	11.96%	307,598	2,264,987	23,465	13.34%
Latvia	86.45%	13.55%	9,224	58,833	692	0.39%
Lithuania	86.15%	13.85%	13,775	85,691	1,031	0.59%
Luxembourg	86.83%	13.17%	1,869	12,324	141	0.08%
Malta	90.38%	9.62%	1,453	13,652	114	0.06%
Netherlands	82.93%	17.07%	89,447	434,636	6,487	3.69%
Portugal	87.02%	12.98%	138,078	926,000	10,425	2.16%
Poland	88.05%	11.95%	49,752	366,537	3,796	5.93%
Romania	87.20%	12.80%	74,080	504,698	5,603	3.19%
Slovakia	87.62%	12.38%	16,908	119,714	1,284	0.73%
Slovenia	86.73%	13.27%	8,904	58,172	670	0.38%
Spain	88.04%	11.96%	204,306	1,503,283	15,584	8.86%
Sweden	82.64%	17.36%	57,017	271,485	4,124	2.34%
United Kingdom	82.36%	17.64%	367,468	1,715,357	26,504	15.07%
Total EU	86.21%	13.79%	2,354,067	14,714,994	175,889	100.00%

Source: Frost & Sullivan analysis

[7] This the expected percent of the target population with severe/late stage AMD given the use of lutein and zeaxanthin

Economic Results

The potential savings from reduced number of severe/late stage AMD case transitions of, ***S***, that is realisable if the entire target population was to utilise a lutein and zeaxanthin regimen can be expressed as:

$$1.\ S = h * A$$

The term ***h*** is the expected per-person cost of a severe/late stage AMD case event and ***A*** is the total number of avoided severe/late stage AMD case transitions in the target population (adults age 50 and older with AMD of any type) yet to be regular users of lutein and zeaxanthin. For the purposes of this case study, we are interested in the total potential cost savings between the extreme scenarios of non-use and 100% use of lutein and zeaxanthin.

There is also a cost of using a lutein and zeaxanthin supplement that must be considered. The net benefits that can be realised from avoided severe/late stage AMD case transitions are:

$$2.\ B = S - C = h * A - Pop * d$$

where ***S*** is the total potential savings from reduced hospital service utilisation following avoided severe/late stage AMD case transitions that are realisable if the entire target population were to utilise lutein and zeaxanthin food supplement daily. The parameter ***C*** is the total population cost of lutein and zeaxanthin utilisation**.** The total cost of a lutein and zeaxanthin utilisation, assuming 100% utilisation by the entire observed population can be represented by ***C=Pop*d*** where ***Pop*** is the total number of people in the target population at risk of experiencing a severe/late stage AMD case-attributed event outcome and ***d*** is the expected per person cost of lutein and zeaxanthin utilisation per year. Note that the entire target population must take the given regimen in order for the total number avoided severe/late stage AMD transitions to be realised. The result of this calculation provides an economic indication of the net monetary benefits ***B*** that the use of lutein and zeaxanthin can yield for society through cost reduction and increased productivity due to avoided long-term home care and loss of life through disability.

Also, it should be noted that equation 2 is a generalised model that determines the net economic effect of using a given food supplement on the odds of a predefined set of event outcomes. Because of the additive nature of the model, one can easily add in additional expected health benefits and costs that are related to the health condition of interest. However, for the purposes of this study, only the potential cost savings due to the relationship between lutein and zeaxanthin food supplement use and severe/late stage AMD case transition reduction was included in the cost equation.

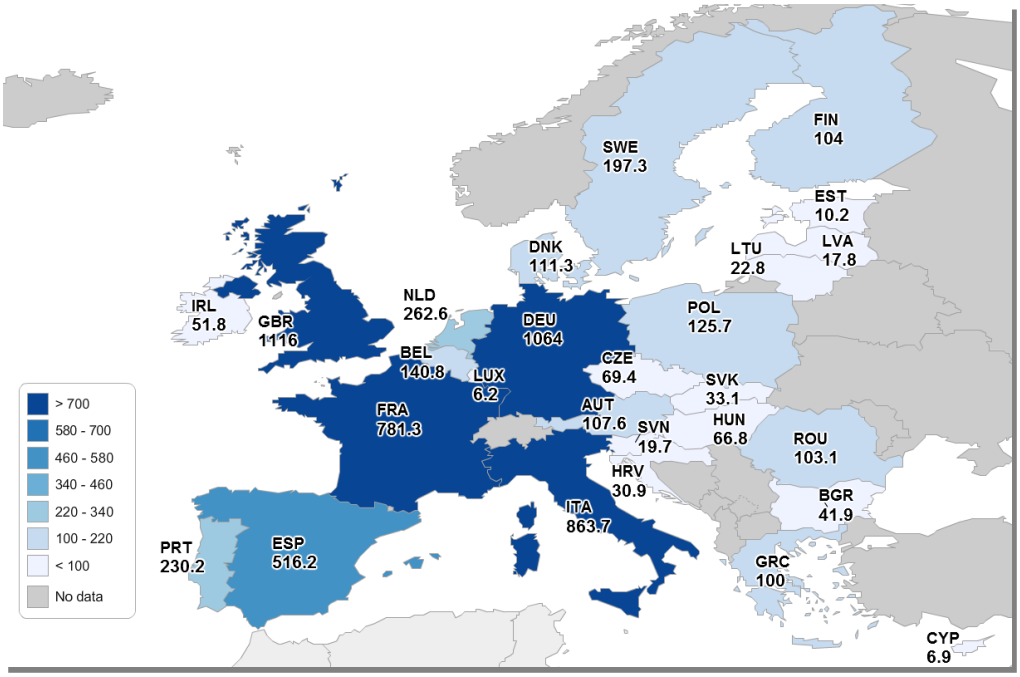
Using the annual average cost per person for a severe/late stage AMD case-related event (€34,805), the total potential avoidable health care cost for all EU adults over the age of 50 with AMD given the use of the lutein and zeaxanthin food supplements would be €6.20 billion per year. Malta has the lowest potential savings (€3.3 million per year) and United Kingdom had the highest potential savings of €1.1 billion in avoided severe/late stage AMD-attributed costs per year. Overall, the five largest EU countries (France, Germany, Italy, Spain, and the UK) can expect potential cost savings in excess of €4.3 billion per year. Table 7 and Chart 3 show the total health care costs savings that are possible from avoided severe/late stage AMD case transitions by EU country.

A total potential of €6.20 billion in avoidable medical costs per year can be realised if all AMD patients used lutein and zeaxanthin in the EU.

Table 7
Economic Benefits from Lutein and Zeaxanthin Food Supplement Use: Total Avoided Healthcare Costs by EU Country, 2016

Country	A: Avoided Case Transitions	h: Estimated PPP-adjusted Cost of AMD per transition per EU Country	S: Expected 1 Year Total Avoided Cost of severe/late stage AMD case Transitions
Austria	2,713	€ 39,677	€ 107,648,303.63
Belgium	3,478	€ 40,487	€ 140,828,969
Bulgaria	2,276	€ 18,403	€ 41,879,088
Croatia	1,400	€ 22,084	€ 30,911,762
Cyprus	207	€ 33,125	€ 6,872,079
Czech Republic	3,144	€ 22,084	€ 69,440,252
Denmark	2,161	€ 51,528	€ 111,347,970
Estonia	394	€ 25,764	€ 10,155,375
Finland	2,354	€ 44,167	€ 103,983,743
France	21,228	€ 36,806	€ 781,322,532
Germany	28,909	€ 36,806	€ 1,064,028,947
Greece	3,397	€ 29,445	€ 100,023,878
Hungary	3,025	€ 22,084	€ 66,799,884
Ireland	1,280	€ 40,487	€ 51,817,262
Italy	23,465	€ 36,806	€ 863,664,735
Latvia	692	€ 25,764	€ 17,839,594
Lithuania	1,031	€ 22,084	€ 22,767,725
Luxembourg	141	€ 44,167	€ 6,221,582
Malta	114	€ 29,445	€ 3,343,410
Netherlands	6,487	€ 40,487	€ 262,645,451
Portugal	10,425	€ 22,084	€ 230,227,669
Poland	3,796	€ 33,125	€ 125,730,113
Romania	5,603	€ 18,403	€ 103,115,875
Slovakia	1,284	€ 25,764	€ 33,090,317
Slovenia	670	€ 29,445	€ 19,736,002
Spain	15,584	€ 33,125	€ 516,239,205
Sweden	4,124	€ 47,848	€ 197,313,234
United Kingdom	26,504	€ 42,106	€ 1,115,994,811
Total EU	175,889	€ 34,805	€ 6,204,989,768

Chart 3
Lutein and Zeaxanthin Supplements Summary Economic Results, Total Potential Health Care Cost Savings, € million, Annualised Average, EU, 2016
Total EU: €6.20 billion



Source: Frost & Sullivan analysis.

The purchase and utilisation of lutein and zeaxanthin food supplements is required to capture the aforementioned healthcare cost savings from avoided severe/late stage AMD case transitions. Based on an author review of lutein and zeaxanthin food supplements sold through online retailers throughout the EU, it is expected that the daily consumer cost of a lutein and zeaxanthin food supplement ranges from as low as € 0.04 per day to more than € 0.85 per day based on a review of lutein and zeaxanthin products sold in Germany, Italy, France, Poland, and the United Kingdom. In many countries in Europe, lutein and zeaxanthin is blended with other health ingredients and supplied to final consumers through specialty eye health formulas. Examples of specialty eye health formulas include the AREDS2 formula[8] or the many eye health product combinations including lutein and zeaxanthin, omega-3 and different vitamins and minerals.[9] The median cost of using lutein and zeaxanthin daily is expected to be approximately € 0.23 per day, or approximately € 84.39 per year.

The purchase and utilisation of lutein and zeaxanthin food supplements is required to capture these potential cost savings from avoided AMD case transitions.

The cost of lutein and zeaxanthin food supplements, like other health care costs, will vary by country. One way to capture this variance is to adjust observed European average market price by the purchasing power of each country's citizens.[10] [30]. Accordingly, the cost of lutein and zeaxanthin utilisation required to realise the expected benefits by the total target population of all adults age 50 and older with AMD at risk of experiencing a severe/late stage AMD case transition per year, **C**, is expected to be € 1.24 billion per year. Table 8 shows the expected daily and annual costs of using lutein and zeaxanthin daily in the EU after ensuring purchasing power parity across all EU countries and the total potential cost of lutein and zeaxanthin food supplements per country.

8 The AREDS 2 formulation includes 500 mg of vitamin C, 400 IU of vitamin E, 80 mg of zinc, 2 mg of copper, 10 mg of lutein, and 2 mg of zeaxanthin.

9 For the purposes of this cost analysis, niche and outlier products were not included in the calculation of the average cost of a daily lutein and zeaxanthin regimen. Examples of these types of products include supplement products where lutein and zeaxanthin make up a small portion of the finished product's formula and relative to value to other health ingredients.

10 According to the World Bank, purchasing power parity (PPP) is a factor that adjusts a given country's domestic value of a Euro required to buy a given product to a baseline country's value of a Euro. For the purposes of this analysis, the purchasing power of a Euro in Belgium was assumed to be 100 versus the other European Union countries [32]. It should be noted that PPP merely reflects the relative value of a Euro across two and more countries and does not establish the baseline value of a Euro. http://data.worldbank.org/indicator/PA.NUS.PPPC.RF.

The median cost of using lutein and zeaxanthin daily is approximately €0.23 per day, or approximately €84 per year.

Table 8
Economic Benefits from Lutein and Zeaxanthin Food Supplement Use: Expected Consumer Price per Lutein and Zeaxanthin Supplements per Day per EU Country, adjusted for Purchasing Power Parity, 2016

Country	d/day: Average Daily Cost of Lutein and Zeaxanthin Food Supplement, € /day	d: Average Annual Cost of Lutein and Zeaxanthin Food Supplement, € /year	PPP: Purchasing Power Parity Weights (Belgium € = 100)	C: Total Cost of Lutein and Zeaxanthin per year
Austria	€ 0.23	€ 83	98	€ 22,010,570
Belgium	€ 0.23	€ 84	100	€ 28,916,213
Bulgaria	€ 0.11	€ 38	45	€ 8,918,351
Croatia	€ 0.13	€ 46	55	€ 6,525,430
Cyprus	€ 0.19	€ 69	82	€ 1,491,452
Czech Republic	€ 0.13	€ 46	55	€ 14,873,917
Denmark	€ 0.29	€ 107	127	€ 18,659,861
Estonia	€ 0.15	€ 54	64	€ 2,162,635
Finland	€ 0.25	€ 92	109	€ 17,252,696
France	€ 0.21	€ 77	91	€ 157,403,639
Germany	€ 0.21	€ 77	91	€ 218,930,657
Greece	€ 0.17	€ 61	73	€ 21,300,560
Hungary	€ 0.13	€ 46	55	€ 14,167,426
Ireland	€ 0.23	€ 84	100	€ 8,778,075
Italy	€ 0.21	€ 77	91	€ 197,354,485
Latvia	€ 0.15	€ 54	64	€ 3,654,677
Lithuania	€ 0.13	€ 46	55	€ 4,578,252
Luxembourg	€ 0.25	€ 92	109	€ 1,306,616
Malta	€ 0.17	€ 61	73	€ 926,989
Netherlands	€ 0.23	€ 84	100	€ 44,225,189
Portugal	€ 0.13	€ 46	82	€ 48,978,080
Poland	€ 0.19	€ 69	55	€ 28,741,889
Romania	€ 0.11	€ 38	45	€ 22,200,326
Slovakia	€ 0.15	€ 54	64	€ 7,336,601
Slovenia	€ 0.17	€ 61	73	€ 4,116,533
Spain	€ 0.19	€ 69	82	€ 117,897,138
Sweden	€ 0.27	€ 100	118	€ 32,761,147
United Kingdom	€ 0.24	€ 88	104	€ 182,791,533
Total EU	€ 0.23	€ 84	--	€ 1,238,260,934

Source: Frost & Sullivan analysis

The total net benefit, B, for the entire EU target population of lutein and zeaxanthin daily users is € 4.97 billion per year. In addition, the benefits per lutein and zeaxanthin user from the target population adults age 50 and older with AMD at risk of experiencing a severe/late stage AMD case transition highly varies and is dependent on relative health care costs in each country and the risk of that given individual experiencing a severe/late stage AMD case-attributed event. Knowing per user benefits is a more useful measure of potential benefits because this statistic can be paired with consumer research insights in order to calculate the portion of the target population who are not current users of lutein and zeaxanthin and who are yet to realise these potential benefits. Overall, the benefit per potential user is expected to be € 291 per user for the EU as a whole. The greatest benefit per user was found to be in Denmark (€ 533 per person per year) which is likely due to this country having a relatively high cost of care for severe/late stage AMD cases, after adjusting for purchasing power parity, and its high severe/late stage AMD case event risk rate. On the other hand, the net benefits per person in Bulgaria and Romania are small, yet still positive, due to the lower health care cost burden these countries have in general even after adjusting for purchasing power parity. It should be noted that this does not mean that these countries would not benefit from using lutein and zeaxanthin supplements daily, because these countries are still avoiding a significant number of severe/late stage AMD case transitions that are directly related to lower productivity, higher long-term care costs, and a lower quality of life. Table 9 and Charts 4 and 5 provide per EU countries details on total severe/late stage AMD case health economic benefits per potential user of a daily lutein and zeaxanthin food supplement.

The benefit per potential user (all adults age 50 and older with severe AMD) is expected to be €291 per user for the EU as a whole.

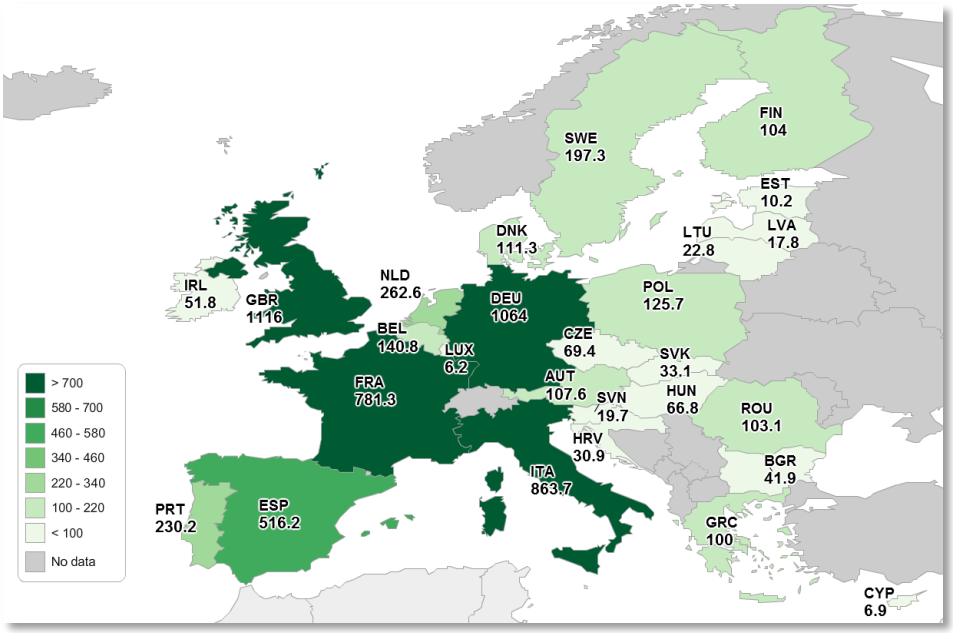
A total net potential of €4.97 billion in avoidable medical costs, after controlling for the cost of the daily use of lutein and zeaxanthin can be realised if all AMD patients used lutein and zeaxanthin in the EU.

Table 9
Avoided Healthcare Costs from Lutein and Zeaxanthin Supplement Use: Avoided Costs of AMD Severity Transitions and Benefits per Target User by EU Country, 2016

Country	B: Expected Net Benefits from Avoided Cost of severe/late stage AMD Transitions	S/Pop: Net Benefit per User (Adjusted Avoided severe/late stage AMD Transition Costs per person per EU country), €/person, Europe, Annualised Average
Austria	€ 85,637,734	€ 321.76
Belgium	€ 111,912,756	€ 326.59
Bulgaria	€ 32,960,737	€ 141.76
Croatia	€ 24,386,332	€ 172.01
Cyprus	€ 5,380,628	€ 249.08
Czech Republic	€ 54,566,335	€ 168.86
Denmark	€ 92,688,109	€ 533.48
Estonia	€ 7,992,740	€ 198.47
Finland	€ 86,731,047	€ 462.78
France	€ 623,918,893	€ 304.08
Germany	€ 845,098,290	€ 296.13
Greece	€ 78,723,318	€ 226.82
Hungary	€ 52,632,458	€ 171.00
Ireland	€ 43,039,187	€ 413.75
Italy	€ 666,310,251	€ 259.00
Latvia	€ 14,184,917	€ 208.43
Lithuania	€ 18,189,473	€ 182.87
Luxembourg	€ 4,914,966	€ 346.28
Malta	€ 2,416,421	€ 159.98
Netherlands	€ 218,420,262	€ 416.77
Portugal	€ 181,249,589	€ 170.33
Poland	€ 96,988,224	€ 232.98
Romania	€ 80,915,548	€ 139.80
Slovakia	€ 25,753,716	€ 188.50
Slovenia	€ 15,619,470	€ 232.86
Spain	€ 398,342,067	€ 233.28
Sweden	€ 164,552,087	€ 500.92
United Kingdom	€ 933,203,279	€ 448.05
Total EU	€ 4,966,728,834	€ 290.98

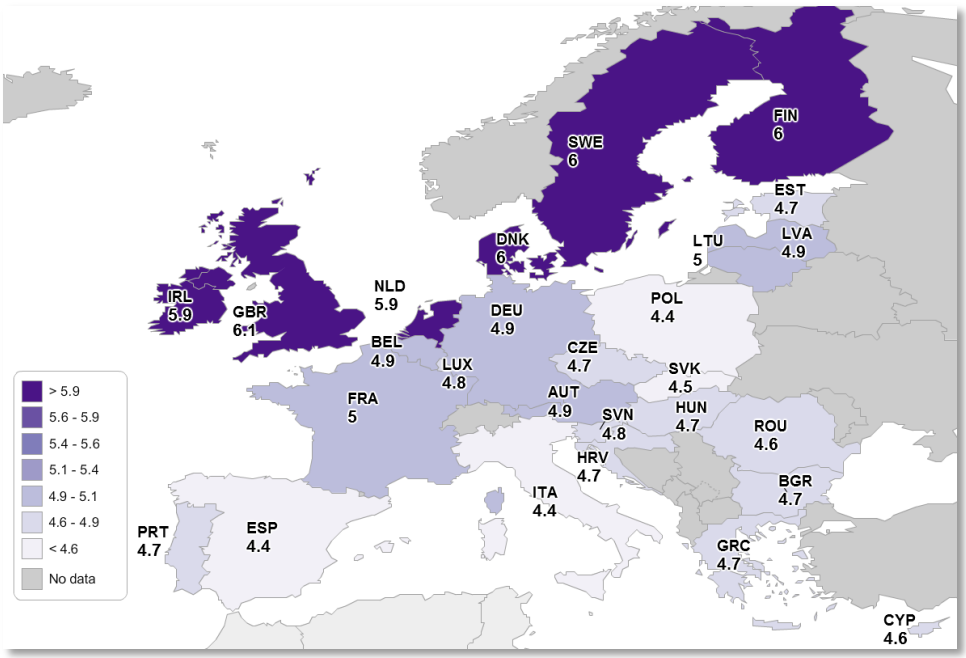
Source: Frost & Sullivan analysis.

Chart 4
Lutein and Zeaxanthin Supplements Summary Economic Results, Total Net Benefits (Potential Health Care Cost Savings Excluding Expected Cost of Supplement), € million, Annualised Average, EU
Total EU: €4.97 billion



Source: Frost & Sullivan analysis.

Chart 5
Lutein and Zeaxanthin Supplements Summary Economic Results, Benefit-Cost Ratio (€ Avoided Costs and Gains per € 1 spent on Lutein & Zeaxanthin Food Supplements) per Country, EU
Total EU: € 5.01 per € 1 spent on Lutein & Zeaxanthin



Source: Frost & Sullivan analysis.

Net health care benefit cost ratio from avoided mild-to-severe AMD transitions is €5.01/€1 spent on a lutein and zeaxanthin supplement regimen per year over the next five years.

As stated, the total net benefit, B, for the entire EU target population of lutein and zeaxanthin daily users is € 4.97 billion per year. This means that for every € 1.00 spent on a lutein and zeaxanthin daily regimen, there would be a certainty equivalent return to the primary payers of health care costs, which include governments and insurance companies, of € 5.01 to society in the form of avoided health care expenditures attributed to severe/late stage AMD case. In fact, all 28 EU countries have benefit cost ratios greater than € 1.00 which is an indication of cost effectiveness as shown in Table 10 below. The greatest net benefit is found in the United Kingdom, where an expected net benefit from avoided severe/late stage AMD case-attributed health care costs is € 933 million per year. Germany and France followed the United Kingdom with € 845 million and € 624 million in per year in total net benefits, respectively.

Table 10
Economic Benefits from Lutein and Zeaxanthin Food Supplement Use: Net Benefit per User (Adjusted Avoided AMD Severity Transition Costs per person per EU country), € 1/person, Europe, Annualised Average

Country	S/C: Benefit Cost Ratio
Austria	€ 4.89
Belgium	€ 4.87
Bulgaria	€ 4.70
Croatia	€ 4.74
Cyprus	€ 4.61
Czech Republic	€ 4.67
Denmark	€ 5.97
Estonia	€ 4.70
Finland	€ 6.03
France	€ 4.96
Germany	€ 4.86
Greece	€ 4.70
Hungary	€ 4.72
Ireland	€ 5.90
Italy	€ 4.38
Latvia	€ 4.88
Lithuania	€ 4.97
Luxembourg	€ 4.76
Malta	€ 3.61
Netherlands	€ 5.94
Portugal	€ 4.70
Poland	€ 4.37
Romania	€ 4.64
Slovakia	€ 4.51
Slovenia	€ 4.79
Spain	€ 4.38
Sweden	€ 6.02
United Kingdom	€ 6.11
Total EU	€ 5.01

Source: Frost & Sullivan analysis

Conclusion

Lutein and zeaxanthin food supplements may provide important potential health care cost savings for all EU adults over the age of 50 with AMD. As indicated in this case study, a considerable amount of scientific research has already been conducted involving lutein and zeaxanthin and there is an indication that this food supplement produces a likely positive impact on the severity of AMD. More scientific research is being conducted to continue to investigate the potential benefits of lutein and zeaxanthin use for eye health in general and reducing the risk of AMD. However, there is a considerable amount of evidence to provide guidance on the magnitude of health care-attributed health and economic benefits that could be realized from the use of lutein and zeaxanthin.

There is significant amount evidence to provide guidance on the magnitude of health care-attributed health and economic benefits that could be realized from the use of lutein and zeaxanthin.

In terms of limitations in the economic approach undertaken in this analysis, the current case study does not follow individual people over time due to data availability limitations. Specifically, this economic model currently treats all of the people in the target population per EU country as a homogeneous set of people, including the expected risk of experiencing an AMD-attributed case transition. Thus, total social benefits are measured and are further distributed across the pre-defined target population. Actual benefits realised per individual user will be a function of the specific AMD case transition risk they face as indicated by their specific risk biomarker levels.

The study focuses on the number of severe transitions that can be avoided, which would lead to an increase of mild cases that may add to the costs. If so, these costs should be controlled for if there is available data on this observation. However, as there is no treatment for dry AMD, these possible costs are not expected to be statistically significant and have thus been omitted from this analysis. Also, the prior cost-benefit analysis makes the conjecture that in the supplementation scenario all adults over the age of 50 with AMD use lutein and zeaxanthin food supplements from a base of zero usage among this population segment. In other words, the calculated net savings is actually the total potential net savings. However, because some adults over the age of 50 are known regular users of lutein and zeaxanthin, a small portion of the target population already has a reduced risk of experiencing a costly AMD case severity transition and is already realising lutein and zeaxanthin's risk-reducing benefits.

Because avoided expenditures and net cost savings are a direct function of the total number of people in the target population using lutein and zeaxanthin food supplements, the calculation of avoided health care expenditures and net cost savings yet to be realised is simply a proportional adjustment of the total potential avoided expenditures and net cost savings. According to the 2012 Council for Responsible Nutrition Consumer Survey on Dietary Supplements, only 4% of U.S. adults over the age of 55 are regular users of lutein and zeaxanthin supplements which implies that the remaining portion of the of target population has not yet realised the potential health, and derived economic, benefits of using lutein and zeaxanthin [31].

Visual acuity (VA) is a good way to measure the severity of AMD and VA's preservation from the use of a scientifically-substantiated food supplement regimen is a key indicator of lutein and zeaxanthin's efficacy.

It is expected that those with mild/intermediate stage AMD are a significant portion of these limited number of users, Moreover, less than 2% of Australians age 55 and older are regular users of lutein and zeaxanthin supplements implying that the rest of the target population has yet to realise the potential benefits of the supplements' regular use [33]. Current lutein and zeaxanthin usage rates per EU country was not readily available for this study, but it is expected that the EU as a whole reflects similar lutein and zeaxanthin consumption trends when compared to the U.S. or Australia. It is also likely that consumption patterns highly vary by EU country. Thus, this is the key reason why benefits per user was calculated so that once consumption trends per EU country are known, calculation of total potential benefits yet to be realised per country can be easily estimated.

In summary, it has been demonstrated in this analysis that there are likely significant health care cost savings to be realised through a concerted effort to identify high AMD risk populations and motivate them to use lutein and zeaxanthin food supplements as a means to help control escalating long-term health care costs. Specifically, this case study shows that there is economic benefit that can be expected from the use of a lutein and zeaxanthin food supplement as a means to reduce the number of AMD cases that transition from the more manageable and less debilitating dry AMD to more severe, and costly, wet AMD among those individuals in the EU with mild/intermediate AMD. As shown, visual acuity (VA) is a good way to measure the severity of AMD and VA's preservation from the use of a lutein and zeaxanthin food supplement regimen is a key indicator of its efficacy. Specifically, this case study provides the key stakeholders—consumers/patients, health care practitioners, governments and regulators, and private payers like health insurance companies—the information they need to make more effective decisions regarding the value of food supplements.

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List of Qualified Studies included in Liu R, Wang T, Zhang B, et al. (2015) Meta-Analysis

Study	Included Studies
1	Piermarocchi S, Saviano S, Parisi V, et al. Carotenoids in Age related Maculopathy Italian Study (CARMIS): two-year results of a randomized study. Eur J Ophthalmol. 2012;22:216–225.
2	Richer SP, Stiles W, Graham-Hoffman K, et al. Randomized, double-blind, placebo-controlled study of zeaxanthin and visual function in patients with atrophic age-related macular degeneration: the Zeaxanthin and Visual Function Study (ZVF) FDA IND #78, 973. Optometry. 2011;82:667–680.
3	Bartlett HE, Eperjesi F. Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular disease: a randomized controlled trial. Eur J Clin Nutr. 2007; 61:1121–1127.
4	Ma L, Yan SF, Huang YM, et al. Effect of lutein and zeaxanthin on macular pigment and visual function in patients with early age-related macular degeneration. Ophthalmology. 2012;119: 2290–2297.
5	Weigert G, Kaya S, Pemp B, et al. Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52:8174–8178.
6	Dawczynski J, Jentsch S, Schweitzer D, Hammer M, Lang GE, Strobel J. Long term effects of lutein, zeaxanthin and omega-3-LCPUFAs supplementation on optical density of macular pigment in AMD patients: the LUTEGA study. Graefes Arch Clin Exp Ophthalmol. 2013;251:2711–2723
7	Murray IJ, Makridaki M, van der Veen RL, Carden D, Parry NR, Berendschot TT. Lutein supplementation over a one-year period in early AMD might have a mild beneficial effect on visual acuity: the CLEAR study. Invest Ophthalmol Vis Sci. 2013;54:1781–1788.
8	Beatty S, Chakravarthy U, Nolan JM, et al. Secondary outcomes in a clinical trial of carotenoids with coantioxidants versus placebo in early age-related macular degeneration. Ophthalmology. 2013;120:600–606.

List of Abbreviations

A	Number of possible avoided events (A) if everybody in a specified target population used Lutein and Zeaxanthin
AREDS2	Age-Related Eye Disease Study II
AMD	Age-related Macular Degeneration
B	Total potential net economic benefits yet to be realised from use of a Lutein and Zeaxanthin food supplement
S/Pop	Benefit per User
C	Total cost of a Lutein and Zeaxanthin regimen
CBA	Cost-benefit analysis
CI	Confidence interval
d	The expected per person cost of Lutein and Zeaxanthin utilisation per year
EFSA	European Food Safety Authority
EU	European Union
g	gram
GBD	Global Burden of Disease
h	The expected cost of a AMD-attributed event
IHME	Institute for Health Metrics and Evaluation
LogMAR	Logarithm of the Minimum Angle of Resolution
mg	milligram
Pop	Target Population
PPP	Purchasing Power parity
RCT	Randomised controlled trials
S	Total potential savings from reduced hospital service utilisation following AMD-attributed hospital events that are realisable if the entire target population were to sufficiently utilise a Lutein and Zeaxanthin food supplement
S/C	Benefit Cost Ratio
S/Pop	Benefit per User
U.S.	United States of America
VA	Visual Acuity
WHO	World Health Organization
x	Share of Population with Mild AMD
y	Share of Population with Severe AMD

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Frost & Sullivan
3211 Scott Blvd, Suite 203
Santa Clara CA, 95054
myfrost@frost.com

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