

TFOS lifestyle: Impact of nutrition on the ocular surface

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ABSTRACT

Nutrients, required by human bodies to perform life-sustaining functions, are obtained from the diet. They are broadly classified into: macronutrients (carbohydrates, lipids, and proteins), micronutrients (vitamins and minerals) and water. All nutrients serve as a source of energy, provide structural support to the body and/or regulate the chemical processes of the body. Food and drinks also consist of non-nutrients that may be beneficial (e.g., antioxidants) or harmful

(e.g., dyes or preservatives added to processed foods) to the body and the ocular surface. There is also a complex interplay between systemic disorders and an individual's nutritional status. Changes in the gut microbiome may lead to alterations at the ocular surface. Poor nutrition may exacerbate select systemic conditions. Similarly, certain systemic conditions may affect the uptake, processing and distribution of nutrients by the body. These disorders may lead to deficiencies of micro- and macro-nutrients that are important in maintaining ocular surface health. Medications used to treat these conditions may also cause ocular surface changes. The prevalence of nutrition-related chronic diseases is climbing worldwide. This report sought to review the evidence supporting the impact of nutrition on the ocular surface, either directly or as a consequence of the chronic diseases that result. To address a key question, a systematic review investigated the effects of intentional food restriction on ocular surface health; of the 25 included studies, most investigated Ramadan fasting (56%), followed by bariatric surgery (16%), anorexia nervosa (16%), but none were judged to be of high quality, with no randomized-controlled trials.

Keywords: diabetes; diet; dry eye disease; food restriction; gut microbiome; keratitis; lifestyle; Mediterranean diet; ocular surface; systematic review

1 INTRODUCTION

Nutrition is a core part of our lifestyle. This report is part of the Tear Film & Ocular Surface Society (TFOS; www.tearfilm.org) Workshop, entitled ‘A Lifestyle Epidemic: Ocular Surface Disease,’ which was undertaken to establish the direct and indirect impacts that everyday lifestyle choices and challenges have on ocular surface health. Poor dietary habits are reported as the second-leading risk factor for deaths and disability-adjusted life-years globally, accounting for 10.3 million deaths and 229.1 million disability-adjusted life-years [1]. The number of people worldwide who are ‘over-nourished’ (those with imbalanced nutrition arising from excessive intake of nutrients) [2] or obese (about 2 billion) now exceeds those who are under-nourished (those not accessing a sufficient number of calories, around 460 million) [3]. However, the over-nourished (from purely an energy perspective) are often under-nourished (from a nutrient perspective) resulting in an epidemic of non-communicable disease characterized by chronic inflammation, impaired immunity, and gut microbiome dysbiosis [4]. Hence, malnutrition in Western countries promotes metabolic disorders and compromised immunity, whereas the under-nourishment in low- to middle-income countries leads to nutritional deficits and associated immunodeficiencies [4]. When a person either does not get enough, or gets too much, of a nutrient, and deficiency or excess is significant over time, the person exhibits signs of malnutrition [5]. With a deficiency of energy, the person may display the symptoms of undernutrition by becoming extremely thin, losing muscle tissue and becoming prone to infection and disease [5]. With an excess of nutritional consumption, the person may become obese and vulnerable to diseases associated with overnutrition, such as heart disease and diabetes [5].

As the prevalence of nutrition-related chronic diseases climbs, it is imperative that the effect of nutrition on the ocular surface, either directly or because of the chronic diseases that result, is understood. The ocular surface is defined as the cornea, limbus, conjunctiva, eyelids and

eyelashes, lacrimal apparatus, and tear film, along with their associated glands and muscular, vascular, lymphatic and neural support. ‘Ocular Surface Disease’ includes established diseases affecting any of the listed structures, as well as etiologically related perturbations and responses associated with these diseases. While certain vitamin deficiencies, such as vitamin A and C, have an established link to ocular surface compromise [6, 7], associations with other systemic nutritional deficiencies are less well established. As understanding increases about the inflammatory mechanisms involved in the etiology of ocular surface disease, questions arise about the impact of systemic inflammatory conditions, diet, and nutrition on the ocular surface. The debate around essential fatty acids and dry eye disease has demonstrated the intense interest of clinicians, researchers and patients in this topic [8, 9].

The purpose of this report is to review the evidence supporting the impact of nutrition on the ocular surface. Relevant evidence is summarized in a narrative style review that, wherever possible, refers to outcomes from high-quality systematic review (Level I) evidence. In alignment with the other TFOS Lifestyle Workshop reports, the Evidence Quality Subcommittee provided a comprehensive database of appraised Level 1 evidence judged to be of potential relevance to the topic area, which was then factored into the writing of the narrative review [10]. In addition, the report includes a systematic review that evaluates the effect(s) of different forms of intentional food restriction on ocular surface health.

2 KEY ELEMENTS OF NUTRITION

A food is defined as any substance, whether processed, semi-processed, or raw, that is intended for human consumption, and includes drinks, food additives, and dietary supplements [11]. Substances used only as drugs, tobacco products and cosmetics (such as lip-care products) that may be ingested are not included in the definition nor in this report. Nutrients, required by the human body to perform life-sustaining functions, are obtained from food. They are broadly

classified into three groups: macronutrients (carbohydrates, lipids, and proteins), micronutrients (vitamins and minerals), and water. Regardless of their class, all nutrients have at least one of three functions: to serve as a source of energy; to provide structural support to the body; to regulate the chemical processes of the body. Consumed food and drinks can also consist of non-nutrients that may be beneficial (e.g., antioxidants) or harmful (e.g., dyes or preservatives added to processed foods).

The sections that follow explore each nutrient class and discuss key variables that influence nutrition in the human body. The goal of these sections is not to provide a comprehensive review of general nutrition, but to define key terminology and provide a foundation to guide the reader through the subsequent sections that consider how nutrition can affect the ocular surface, a site seemingly far removed from the digestive tract.

2.1 Macronutrients

Macronutrients consist of carbohydrates, lipids (also called fats) and proteins and have two critical attributes in common. First, all macronutrient classes are required by the body in large quantities [12]. Second, all macronutrients are capable of serving as an energy source, which is typically measured in units of kilojoules per gram [12].

2.1.1 Carbohydrates

Carbohydrates consist only of carbon, hydrogen and oxygen [13]. Their primary role is to provide energy, though they also support the functions of a variety of other organ systems [12]. Major dietary sources of carbohydrates are grains, dairy products, fruits and starchy vegetables.

Carbohydrates are further classified as being either simple or complex. Simple carbohydrates contain up to two monosaccharides and include sucrose and glucose (the primary sugar utilized by the human body) [12]. Complex carbohydrates, such as glycogen and starch, contain branched or unbranched chains of many simple carbohydrates [12]. During digestion,

simple sugars (glucose primarily) are released to fuel cells in the body. The effect of consumed carbohydrates and sugars on the ocular surface is considered in Section 3.1.1.

Fiber is a unique, complex carbohydrate. It is non-digestible and therefore passes through the digestive tract unaltered by human cells of the gastrointestinal system, yet it is needed to help regulate blood sugar and the sensation of hunger [12]. The gut microbiome is capable of breaking down fiber into absorbable simple carbohydrates [12]. Section 3.9 further explores the impact of the gut microbiome on nutrition and its potential effects on the health of the ocular surface.

2.1.2 Lipids

Lipids are composed of carbon, hydrogen and oxygen, and have a primary responsibility of providing (or storing) energy [12]. Lipids also have a role in cell membrane structure, organ protection and temperature regulation [12]. Unlike carbohydrates, lipids are insoluble in water, due mostly to the hydrocarbon tails of their component fatty acids, the basic subunit of a lipid molecule. Major dietary sources of lipids include meats, fish, dairy products, butter, oils and nuts.

Lipids can be classified into saturated or unsaturated varieties. Saturated lipids are those in which each carbon of the hydrocarbon tail is saturated with hydrogen (i.e., the hydrocarbon tails lack double bonds). Unsaturated lipids have one (monounsaturated) or more (polyunsaturated) double bonds in the hydrocarbon tails and are therefore not saturated with hydrogen. Two important lipid classes that have been the source of significant investigation with respect to their role in ocular surface health are omega-3 (n-3) and omega-6 (n-6) fatty acids. Both omega-3 and omega-6 fatty acids must be consumed in the diet, as the human body is incapable of synthesizing them *de novo*. Both share the same enzyme system, creating a competitive environment that is either primarily pro-inflammatory (in diets dominated by omega-6 fatty acids) or anti-inflammatory (in diets dominated by omega-3 fatty acids). The

effects of dietary omega-3 and omega-6 fatty acids on the ocular surface have been comprehensively reviewed elsewhere [9, 14-20] and are further discussed in sections 3.1.1.1 and 3.4.6.

2.1.3 Proteins

On an elemental level, proteins differ from the other two macromolecules because they contain nitrogen in addition to carbon, hydrogen and oxygen [12]. Proteins are composed of amino acid subunits. While proteins are capable of serving as an energy source, their primary function is to provide structural support to muscles, bones and skin, and to facilitate most of the chemical reactions that occur in the body by acting as enzymes [12]. Major dietary sources of proteins include meats, dairy products, seafood, and many types of plant-based foods (e.g., lentils, beans, peas and soy).

2.2 Micronutrients

In contrast to macronutrients, micronutrients are needed in much lower quantities and do not serve as energy sources. This group consists of vitamins and minerals, both of which often serve as co-factors or co-enzymes that are essential to execute many bodily functions. There are 13 essential vitamins that are subdivided into those that are soluble in water and those that are soluble in fat [5]. The water-soluble vitamins are thiamin (B₁), riboflavin (B₂), niacin (B₃), pantothenic acid (B₅), pyridoxine (B₆), biotin (B₇), folate (B₉), cobalamin (B₁₂) and ascorbic acid (C) [12]. The fat-soluble vitamins are A, D, E and K [12]. Minerals are solid inorganic substances that perform a wide variety of functions in the human body. There are 16 essential minerals that are subdivided into those needed in larger quantities (seven macrominerals) and smaller quantities (nine trace minerals). Macrominerals are sodium, chloride, potassium, calcium, phosphorus, magnesium and sulfur. Trace minerals are iron, zinc, iodine, selenium, copper, manganese, fluoride, chromium and molybdenum [12]. Other trace nutrients known to

be essential in small amounts include nickel, silicon, vanadium and cobalt [21]. The effects of select vitamins and minerals, including their deficiencies and supplementation, on the ocular surface are further discussed in sections 3.1.2, 3.4.5 and 3.4.9.

2.3 Hydration

Water is a critical component of the diet. There are four overarching functions attributed to water: to serve as a vehicle for transport, as a neutral medium for biochemical reactions, as a source of lubrication or shock absorption, and as a regulator of body temperature [12]. To support these functions, the Food and Nutrition Board of the Institute of Medicine recommends that adult males consume 3.0 liters and adult females consume 2.2 liters of water per day [22].

Water is continuously transported into and out of the organ systems of the body, creating specialized compartments with their own specific solute concentrations. Though water itself moves passively in the human body, the driving force for the water movement is actively regulated by creating chemical gradients across semi-permeable membranes. These gradients are provided by differences in concentrations of electrolytes, or charged ions dissolved in water. Most macrominerals are electrolytes; sodium and chloride, the components of table salt, are among the most important [12]. Salt intake, therefore, plays a major role in osmoregulation, defined as the tight control of fluid balance throughout the body. Considering that the tear film is mostly water, the hydration status of the body has been purported to influence tear and ocular surface physiology [23]. This topic is further discussed in section 3.2.

2.4 Excipients, additives and non-nutritional components

Processed foods are those that have been subject to any amount of change from their natural state. Simply cooking a food, for example, is one form of processing a food. Ultra-processed food, however, comprises a class of processed foods that includes the addition of artificial colors, flavors, sweeteners, emulsifiers, thickeners, preservatives or other chemicals [24].

A food excipient is any substance that has no bioactivity itself, but is added to promote the bio-activity of co-ingested active ingredients [25]. Non-nutritional chemicals present in food may include food additives or contaminants, the latter often originating from environmental pollution. Some of these chemicals may have toxicological properties. Food additives are added to improve freshness, flavor, texture or appearance. They may be synthetic or natural, deriving from plants, animals or minerals [26]. Contaminants in food can occur because of environmental pollution (e.g., via water, soil or air), or as a result of food production. Examples of contaminants are metals, dioxins and polychlorinated biphenyls [27]. Materials used in food packaging such as cans and bottles may contain chemical substances that can leach into food. Also, the use of pesticides and the production or manufacturing processes of food can lead to the presence of unwanted chemicals in food [27]. Some of these non-nutritional chemicals may have bioactivity in the human body and on the ocular surface, as discussed in section 3.3.

2.5 Whole foods versus nutrient extracts

Food, in all its complexity, is a more fundamental unit than any individual nutrient [28]. Whole foods represent complexes of macronutrients, micronutrients, bioactive compounds and their concomitant interactions, and hence, identifying the effects of single dietary nutrients within or without the context of the overall diet is very challenging [29, 30]. Adding to this complexity, the human gut microbiome uses nutrients as metabolic precursors, altering nutritional content as different bacteria synthesize or access nutrients from the host diet [29].

The discovery that certain health conditions are caused by deficiency in a single nutrient and can be cured by providing the deficient nutrient in isolation were watershed for public health. Examples include scurvy and ascorbic acid, pellagra and niacin, beriberi and thiamine, rickets and vitamin D, and neural tube defects and folic acid [31]. Dietary supplements may be used with the intent of mitigating, treating or preventing disease [32], although the regulatory requirements for dietary supplements differ significantly from medicines, and many such

applications may not be supported by high-quality clinical evidence as discussed in section 3.4 [30]. There can be further concerns in the provision of supplements including, but not limited to: identification of the authentic source of the raw materials, purity, presence of other active compounds, quality, lack of experimental evidence, false advertising, contamination and interactions between supplements and drugs [32]. Hence, in relation to chronic disease prevention, diets or diet remedies that focus on single nutrients can be seen as illustrations of the inadequacy of a primarily reductionist approach [33]. Extracted nutrients lacking the coordination inherent in whole foods and clinical trials frequently failing to demonstrate efficacy of isolated nutrients [31], support the concept of food synergy as worthy of more research [34].

Supplements for which there is sufficient evidence to suggest positive contribution to micronutrition will be discussed in detail in section 3.4.

2.6 Over-nutrition

Under-nutrition is ceding to over-nutrition and shifting disease burden from infection to non-communicable diseases in both developed and developing countries [35]. Dietary patterns are reflecting increased consumption of energy-dense “convenient”, ultra-processed, and “fast” (in the sense of quick rather than food restriction) foods [36].

Over-nutrition is a complex issue involving neuro-endocrine signalling, gut microbiome and dysregulation of lipid and glucose metabolism [37]. Chronic over-nutrition creates an environment of systemic inflammation that leads to “overstimulation-induced insensitivity,” a phenomenon commonly present in obesity and metabolic disorders [38]. Obesity, which often results from over-nutrition, is defined by excessive body weight composed of an accumulation of energy reserves as fat deposits [39]. This chronic adiposity leads to impaired glucose, lipid and protein metabolism triggering chronic, systemic, low-grade inflammation that renders cells insensitive to hormonal regulation [36, 38]. Metabolic syndrome is a cluster of interrelated

metabolic abnormalities including insulin resistance, hyperglycemia and hyperlipidemia, discussed in section 4.1.3 [40]. A hallmark of metabolic syndrome resulting from over-nutrition is the accumulation of adipose tissue, that is then infiltrated by immune cells, leading to low-grade chronic inflammation [40]. All of these are characterized as chronic diseases into which certain ocular surface diseases are increasingly being categorized.

2.7 Caloric restriction

Caloric restriction consists of the chronic reduction of total calorie intake without malnutrition [41], which can exert a potent anti-inflammatory effect that alters the cellular metabolism and gut microbiome to reduce oxidative damage and inflammation [42]. Additionally, caloric restriction causes increased presence of commensal bacteria that produce short chain fatty acids leading to improved intestinal integrity [42]. Caloric restriction induces the decrease of anabolic hormones (such as insulin and growth hormone), inhibition of the mitogen-activated protein kinase pathway, suppression of inflammation by downregulation of interferon and pro-inflammatory cytokines, and reduction of reactive oxygen species [42].

The lived experience of dietary restriction overlaps with cultural loci for centenarian eating patterns, such as in Okinawa in Japan [43]. Hence, regulation of chronic inflammation through a caloric-restricted diet offers an alternative to pharmacological and procedural interventions for chronic Western disorders. This is further discussed in sections 3.8.2 and 6.

2.8 Factors influencing nutrition

2.8.1 Age

The aging adult body experiences dramatic changes in bone density, muscle tone, fat distribution, reproductive physiology and digestive physiology, among other changes. In young adulthood, defined as between the ages of 19 and 30 years, the body is usually relatively stable [12], except for women who experience pregnancy, childbirth, and lactation. Peak health and

fitness are typically achieved at this age, particularly in the active adult with a well-balanced diet. Middle age, which extends from ages 31 to 50 years, is as dynamic as the former is stable [12]. Older adulthood extends from age 51 years until death and is marked by decreasing hormone levels, redistribution of fat, and thinner and less resilient skin in older adulthood [12]. Even in the absence of renal disease, kidney function declines, which can affect electrolyte composition and interfere with optimal hydration [12]. The gastrointestinal tract also becomes less efficient in absorbing essential vitamins and minerals, potentially predisposing to deficiencies [12].

2.8.2 Sex

Many government regulatory bodies, such as those of the UK [44], European Union [45], USA and Canada [46-49], have recommended dietary intake values for many macronutrients and micronutrients. Different values are typically recommended for males and females across the lifespan. Biological sex, however, is usually a confounding variable, as body weight is the primary differentiating factor between the varying recommendations for male and female adults [50].

2.8.3 Ethnicity

Diet and specific foods are often rooted in cultural norms [51]. Conversely, dietary acculturation, common to immigrants and indigenous populations, is the adoption of dietary practices of the dominant culture within which varying degrees of maintenance of traditional practices yield diverse health outcomes [52-55]. For example, people with Hispanic ethnicity adopting the culture of the USA and reducing the influence of their traditional culture are reported to appropriate a diet of reduced quality relative to those who retain their traditional culture [56]. A systematic review of such practices [57] reported accumulating evidence suggesting people of Hispanic ethnicity born in the USA, speaking predominantly English,

and/or assuming the dominant culture of the USA (as determined through acculturation scales), generally consumed fewer fruits and vegetables, but more salt, added sugar and calories from fat, and ate more away-from-home meals than those less assimilated [57].

The most common reported dietary change in immigrants to the USA is increased consumption of red meat and junk/fast foods (energy-dense foods high in fat and sugar and low in nutrients contributing to the daily energy at affordable cost [5]) and an associated increase in body mass index (BMI) [58].

2.8.4 Socioeconomic factors

It has been well documented that in affluent countries, poor health and diet quality are associated with low socioeconomic status, with similar findings increasingly reported in low- and middle-income countries. These findings suggest that socioeconomic factors have an independent deleterious effect on diet [59].

Adults in the USA with higher income are reported to have greater compliance to dietary guidelines [60]. The lower diet quality index measured in low-income communities could be ascribed to limited access to healthier food due to the cost and access to facilities to prepare, raising the spectre of increased food insecurity in lower socioeconomic status groups [61].

Level of education can affect not only purchasing ability related to income, but also exposure to, and understanding of, dietary information. The National Health and Nutrition Examination Surveys conducted in the USA from 1971 to 2002 suggest that although total energy intake or amount of foods consumed appeared to differ little by education, intake of micronutrients, fruits and vegetables were reduced with lower level of education in all surveys [62]. Generally, increased consumption of fish, nuts and seeds along with reduced red and processed meat are seen in more highly-educated individuals and women, which has been suggested to be driven by both health and climate change concerns [63].

Poor dietary habits and an increased prevalence of non-communicable disease are also of concern for developing economies undergoing ‘nutrition transition,’ such as parts of Asia, Africa, the Middle East and Latin America [64]. This has also been shown in adolescent boys in China adopting the fast-food habits of those in lower socioeconomic groups in developed countries [65]. These findings suggest that there is a transitional adoption of lower socioeconomic nutrient patterns during periods of accelerated economic growth [64].

In 2018, more than 50% of adults in the USA reported consuming three or more meals out-of-home per week [64]. Australia also reported that more socioeconomically disadvantaged groups tended towards less healthy foods when away from home [64]. Fast food tends to be low in whole grains, fruit, vegetables, nuts and seeds, but high in sugar, sodium and processed meat, which, along with high intakes of alcohol, are leading factors in early death and disability [63]. Studies in Europe, the USA, Australia, New Zealand, and increasingly in Asia, find that lower socioeconomic status is associated with increased frequency of out-of-home meals, with those living in the poorest areas having a higher exposure to fast food outlets than those in less deprived areas [64]. Overall, the literature overwhelmingly suggests that those from lower socioeconomic groups are more susceptible to inequalities in diet with a concomitant increase in obesity and chronic disease [64].

3 NUTRITION AND THE OCULAR SURFACE

3.1 Nutrition

In considering what constitutes a diet optimal for ocular surface health, this section of the report considers each element of nutrition and its known impact on the ocular surface.

It is important to be mindful that when discussing individual dietary elements, the whole (potential dietary interactions of the whole foods) is more influential than the sum of its

individual parts. Investigating single nutritive substances in isolation can therefore be fraught with inconsistencies or misguided conclusions [66], as discussed in section 2.5.

Where specific studies of macronutrients pertaining to ocular surface health have been reported, these are discussed within their context. However, for many of the food groups, their relationship to gut dysbiosis and chronic inflammation is the focus, with the attendant inflammation associated with ocular surface disease as discussed in section 3.9.

3.1.1 Macronutrients

3.1.1.1 Polyunsaturated fatty acids

As mentioned in section 2.1, omega-3 polyunsaturated fatty acids include α -linolenic acid, eicosapentaenoic acid and docosahexaenoic acid, while omega-6 polyunsaturated fatty acids include linoleic acid, dihomo- γ -linolenic acid and arachidonic acid [67]. In relation to resolution of ocular surface inflammatory disorders, research using a mouse dry eye model demonstrated that resolvins and protectins (derivatives of omega-3 polyunsaturated fatty acids that help resolve acute inflammation [68]) inhibit leukocyte infiltration and enhance macrophage activity, leading to increased corneal epithelial integrity and increased tear production [69-71]. Docosahexaenoic acid-generated neuroprotectin D1 plays a role in controlling ocular surface inflammation, in addition to offering neuroprotection [72]. Corneal neurogenic health is essential for ocular surface health and neurotrophic keratitis can arise when corneal nerves are damaged. Spontaneous epithelial breakdown, impaired wound healing and corneal ulceration result when tear production and reflex blinking are impaired [72]. A study on 26 individuals with diabetes and 21 healthy controls reported a positive relationship between the systemic Omega-3 Index and corneal nerve parameters [73], suggesting that omega-3 intake may impact corneal neural health.

A cross-sectional study of 32,470 women aged 45 to 84 years who were health professionals in the Women's Health Study [74] identified 1,546 (4.7%) participants who

reported a clinical diagnosis of dry eye disease. After adjusting for demographic factors, hormone therapy and total fat intake, the odds ratio (95% confidence interval [CI]) for the highest versus lowest fifth of omega-3 fatty acids was 0.83 (0.70-0.98), $p = 0.05$ and a higher ratio of omega-6 to omega-3 fatty acid consumption was associated with significantly increased risk of dry eye disease, odds ratio (CI) = 2.51 (1.13-5.58) for > 15 to 1 versus <4 to 1 ($p = 0.01$). In addition, tuna consumption was inversely associated with dry eye disease (odds ratio = 0.81, CI = 0.66-0.99 for 2-4 113 g (4 oz) servings/week, and odds ratio = 0.32, CI = 0.13-0.79 for 5-6 servings/week versus ≤ 1 servings/week; $p = 0.005$). Overall, a higher dietary intake of omega-3 fatty acids was associated with a decreased presence of dry eye disease in women.

Further evidence that omega-3 deficiency results in ocular surface sequelae is shown in sometimes conflicting evidence of omega-3 fatty acids having a role in the management of dry eye disease [75]. Omega-3 fatty acid supplementation is further discussed in section 3.4.6.

3.1.1.2 Vegetable oils and seeds

3.1.1.2.1 Olive oil

Direct evidence for extra virgin olive oil contributing to ocular surface health is lacking. Extra virgin olive oil has been chosen as the placebo for a number of studies investigating the effects of oral omega-3 fatty acids on ocular surface health [76-82] and whether this could have been a confounding factor in these analyses is likely to be dose dependent and is discussed in section 3.4.6.1.4.

3.1.1.2.2 Flaxseed oil

Flaxseed oil is composed of approximately 50% α -linolenic acid (a short-chain omega-3 fatty acid). Studies of flaxseed ingestion for treating ocular surface disease are discussed further in section 3.4.6.

3.1.1.2.3 Primrose oil

Primrose oil is a rich source of omega-6 fatty acids. A review of clinical trials of oral primrose oil suggested that overall there were possible improvements in ocular comfort and inflammation, but cited limitations in study design that might have confounded the results [83].

3.1.1.2.4 Palm oil, soybean oil, hydrogenated vegetable oils

In contrast to olive oil and flaxseed oils, vegetable oils such as palm, corn, soybean, cottonseed, safflower, sunflower and hydrogenated vegetable oils are low in omega-3 and high in omega-6 fatty acids. Ingestion of these oils may contribute to a suboptimal omega-6 to omega-3 ratio in the overall diet, which can predispose the body to chronic inflammation [84]. In addition, consumption of *trans* fatty acids, produced by the partial hydrogenation of vegetable oils, is associated with greater levels of systemic inflammation in women [85]. Independent of other risk factors, higher intake of *trans* fat and lower intakes of polyunsaturated fat increase the risk of type 2 diabetes [86], and as type 2 diabetes can affect the ocular surface (section 4.1.4) there may be a link between *trans* fats and ocular surface health.

3.1.1.3 Sugars and artificial sweeteners

The less refined a naturally occurring sugar source, the greater is its nutritive value [87]. For example, Turbinado sugar is the least refined sugar, which, along with blackstrap molasses (both from sugar cane), contains significant amounts of calcium, magnesium, potassium and iron. Agave nectar contains trace amounts of iron, calcium, potassium and magnesium, but also contains a significant concentration of fructose, higher than high fructose corn syrup which has been associated with inducing abdominal fat, high triglycerides, heart disease and insulin resistance [88]. There is no direct evidence of its impact on the ocular surface.

Artificial sweeteners are categorized into two groups: nutritive sweeteners (or low calorie), which add some energy value (calories) to food, or highly concentrated non-nutritive

sweeteners that add no caloric value, since they are used in small quantities [87]. For the most part, artificial sweeteners are not utilized by the human body and hence were long considered a useful weight loss tool with minimal metabolic effects. Some epidemiological studies have shown that artificial sweeteners can aid in weight loss for those who experience glucose intolerance and type 2 diabetes [89]. However, an increasing number of studies now suggest that artificial sweeteners induce metabolic syndrome (see section 2.6) and development of glucose intolerance and weight gains, which may be partly due to perturbation of the gut microbiome [90]. Such deleterious interventions can subsequently lead to an inflammatory response, dysbiosis and metabolic disorders [91], although there is no evidence of direct impact on the ocular surface.

3.1.1.4 Gluten

Gluten, a complex mixture of glutamine- and proline-rich proteins, is found in some cereals. Gluten-free diets are supported in the treatment of celiac disease, possibly also in allergies against wheat, in some chronic diseases including rheumatoid arthritis, and inflammatory bowel disease [92]. The danger of gluten-free diets in healthy populations is that it excludes many complex carbohydrates, and may result in nutrient deficiencies of fiber and certain vitamins and minerals, with a potential trade-off in increased fats and sugars contained in processed gluten-free products. This has an associated increased inflammatory potential [92] with evidence of nutritional deficiencies of such diets leading to impaired bone health, and reproductive anomalies and increased risk of metabolic syndrome [93]. Although ocular surface inflammation can develop in individuals with celiac disease, this appears to be due predominantly to mechanisms reported for other chronic or autoimmune disorders, and eliminating gluten from the diet might reduce ocular surface inflammation due to an overall reduction of exacerbation of the disease [94]. There is no direct evidence of the impact of gluten, or its absence, on the ocular surface.

3.1.2 Micronutrients

Deficiencies in iron, vitamin A and iodine are the most common deficiencies around the world, particularly in children and pregnant women [95]. At least half of the children worldwide, younger than 5 years of age, suffer from vitamin and mineral deficiencies [95]. Low- and middle-income countries bear a disproportionate burden of micronutrient deficiencies [95]. In the homeostasis of the ocular surface, micronutrients play an important role [95]. Their impact on the ocular surface is discussed in the next section, and the impact of their supplementation is discussed in section 3.4.

3.1.2.1 Vitamins

The major vitamins associated with ocular surface diseases are vitamin A, B₁₂, C and D [96].

3.1.2.1.1 Vitamin A

Vitamin A is a group of nutritional organic compounds that includes retinol, retinal (from animal sources) and several provitamin A carotenoids (especially beta-carotene) that can be found in fruit and vegetables. It is essential for the maintenance of the immune system, growth and development, including metabolism and differentiation of the ocular surface epithelium [97]. Vitamin A has a complex mechanism of action, such as upregulating the cytochrome P450 synthesis of eicosanoids in *in vitro* human models of the conjunctiva and cornea [98]. Vitamin A also stimulates the synthesis of mucin 4 (MUC4) that is present on conjunctival epithelial cells [99]. Additionally, vitamin A has been shown to be involved in the down-regulation of androgen receptor expression on the ocular surface [100]. In a rat dry eye model, overexpression of keratinocyte transglutaminase was found to be associated with the abnormal keratinization of the cornea due to vitamin A-deficiency [101]. This is further reviewed in the Elective Medications & Procedures report [102] and elsewhere [103].

Deficiency of vitamin A is the most frequent form of malnutrition that contributes to ocular disease in the developing world; it is also the major cause of childhood blindness in the world [104, 105]. Vitamin A deficiency causes ocular surface changes such as decreased or absent goblet cells, xerophthalmia and corneal punctate keratopathy [106, 107]. Long-term vitamin A deficiency causes epithelial metaplasia and keratinization, leading to xerophthalmia, Bitot's dots, keratomalacia and corneal perforation [108].

3.1.2.1.2 Vitamin B₁₂

Vitamin B₁₂, also known as cobalamin, is a cofactor in DNA synthesis, in fatty acid metabolism and amino acid metabolism. Vitamin B₁₂ can be found in foods such as meat, fish and dairy products. It is the only vitamin that contains a metal ion, cobalt. Vitamin B₁₂ is indispensable for erythrocyte and leukocyte production. Together with folic acid, this vitamin contributes to the synthesis of DNA, amino acids and bone marrow proteins. It is also necessary for the normal functioning of the alimentary tract and nervous system. Vitamin B₁₂ plays an essential role in the synthesis of myelin, and its deficiency is connected with myelopathy, peripheral neuropathy and optic atrophy [109]. In the USA, it has been demonstrated that the prevalence of vitamin B₁₂ deficiency varies by age range, affecting at least 3% of those aged 20–39 years old, 4% of those aged 40–59 years and 6% of those 60 years or over [110].

In a population-based cohort study, vitamin B₁₂ deficiency was found to be associated with a 1.6 times increased risk of having dry eye disease ($p = 0.002$) [111].

3.1.2.1.3 Vitamin C

Vitamin C, also known as L-ascorbic acid, is necessary for the biosynthesis of collagen, L-carnitine and protein metabolism [112]. It is an important physiological antioxidant and regenerates other antioxidants, including vitamin E [112]. Vitamin C also plays a crucial role

in immunological processes and improves the absorption of iron [113]. This vitamin cannot be synthesized endogenously by humans and its best sources are fruits and vegetables [114].

Vitamin C can be found in tears, and possibly is involved in antioxidant defense [115]. Moreover, vitamin C has a role in corneal healing after injury [116].

3.1.2.1.4 Vitamin D

Vitamin D plays a crucial role in several biological functions, including calcium homeostasis, immune regulation, cellular proliferation, differentiation and apoptosis, and angiogenesis. Vitamin D is obtained from dietary consumption and is produced in the skin after direct sunlight exposure [117]. Its level in human tears is higher than in serum [118]. In the human cornea, this vitamin undergoes active metabolism due to the presence of 1-alpha-hydroxylase, the key enzyme that activates vitamin D₃ to calcitriol, its active metabolite [119].

Vitamin D deficiency has been related to the pathogenesis of dry eye disease [120], in particular conjunctival squamous metaplasia and a loss of conjunctival goblet cells [121]. Additionally, vitamin D has been implicated in the modulation of systemic calcium absorption that promotes fluid secretion in the salivary and lacrimal glands [122]. A significant correlation has been found between serum vitamin D levels and tear production, stability and ocular dryness symptoms [123]. Systematic review and meta-analysis studies have reported that vitamin D deficiency is associated with the exacerbation and onset of dryness symptoms [124-126].

3.1.2.2 Minerals

Selenium is an essential micronutrient that shows a synergistic action with vitamin E as an antioxidant [5]. It protects cells, cellular membranes, mitochondrial membranes and DNA against the harmful effects of free oxygen radicals. The main dietary sources of selenium are Brazil nuts, meat, fish, seafood and cereals. The biological effects of selenium are largely mediated by selenium-containing proteins (selenoproteins) [127]. In the group of

selenoproteins, selenoprotein P is generated by the lacrimal gland and secreted in tears, providing selenium to the corneal epithelium [128]. In dry eye disease, the level of selenoprotein P in tears has been found to be decreased, with selenium deficiency thought to result in oxidative damage to the ocular surface [128].

Lactoferrin occurs naturally as an iron-binding glycoprotein. It is produced and secreted by mucosal epithelial cells and neutrophils in mammalian species, including humans. It is typically present in fluids such as milk, saliva and tears. As lactoferrin shows anti-inflammatory, antioxidant and antimicrobial effects, its topical application may help maintain a healthy ocular surface system. One study reported a relationship between low levels of tear lactoferrin, and the development of dry eye disease and chronic meibomitis [129].

Lower serum levels of zinc, copper, and selenium were found in 50 patients with advanced keratoconus compared to 50 healthy controls, suggesting a possible role of antioxidant activity of these trace elements in the etiology of advanced keratoconus and a possible role as a treatment option [130]. Previous studies have suggested enzymatic roles of these elements in connective tissue metabolism leading to oxidative stress in tissues, abnormal collagen synthesis and impaired breakdown of collagen [130]. No trials have yet been performed to consider an effect of mineral supplementation in reducing the progression of keratoconus.

3.2 Hydration

Sufficient hydration is essential for the optimal functioning of the human body including physical and cognitive performance [131-133]. Increasing water intake has been associated with health benefits, such as increased skin hydration [134] and reduced exercise-related asthma and urolithiasis [135]. However, to-date there have been few studies that have assessed the role of hydration status or water intake on ocular surface health, including in individuals with dry eye disease.

Two studies reported a link between plasma osmolality, a marker of general hydration, and tear osmolality [136, 137]. The first, a hospital-based cross-sectional study (n = 111), found that patients with dry eye (defined by tear osmolality, tear breakup time (TBUT) and dry eye symptoms) had a higher plasma osmolality than a non-dry eye control group [136]. The second, a smaller study (n = 14), found plasma osmolality and tear osmolality to be strongly correlated ($r = 0.93$) in healthy volunteers who exercised in heat with fluid restriction [137]. The authors speculated that dehydration may increase tear osmolality through decreased lacrimal gland function [137]. No clinical trials have specifically investigated the effect of water intake on ocular surface parameters. A randomized clinical trial that considered the effect of oral caffeine consumption on tear production found no change in Schirmer score results relative to the control group who drank 200 mL of water only (tested between 45 and 180 minutes after consumption) [138]. A population-based study including 51,551 participants in the Netherlands investigated the association between both water intake (from all dietary sources assessed by food frequency questionnaires) and 24 hour urine volume as markers of systemic hydration and dry eye as an outcome variable [139]. Neither water intake nor urine volume was associated with a protective risk of dry eye (either a clinical diagnosis or dry eye symptoms). Results did not change after accounting for more than 70 comorbidities and medications [139].

Drinking more water for dry eye has been used as an adjunct management strategy for patients and may also be recommended by some clinicians [137, 140]. However, based on the current limited studies, increased water intake has not been directly tied to improved dry eye or ocular surface outcomes. Future longitudinal studies should investigate whether increasing water intake is beneficial in patients with dry eye disease.

3.3 Excipients, additives and non-nutritional components

3.3.1 Endocrine-disrupting chemicals

As discussed in the TFOS Lifestyle Environmental Impact Report [141], endocrine-disrupting chemicals, also referred to as endocrine disruptors, are compounds that can bind to the hormone receptors of cells to activate or block the action or interfere with the synthesis, secretion or transport of hormones [142, 143]. Endocrine-disrupting chemicals can affect various hormones, including sex hormones, which are particularly important in ocular surface health [144]. The main source of endocrine-disrupting chemical exposure for humans is by ingestion, e.g., via pesticides that end up in the food chain, and leaching from food containers or contamination during manufacturing or processing of foods. Examples of endocrine-disrupting chemicals that are commonly found in products are bisphenols A, S and F, alkylphenols, dichlorodiphenyltrichloroethane, phthalates and parabens [145].

A systematic review on the effects of endocrine-disrupting chemicals on the human microbiome concluded that there is growing evidence of these chemicals changing the diversity of resident microbiota, including the gut microbiome [146]. A study looking at exposure to the organophosphate azinphos-methyl, an insecticide, in farmworkers found significant alterations of the oral buccal microbiota with less bacterial diversity after exposure [147]. Studies on the effect of the many endocrine-disrupting chemicals in ocular surface disease are lacking. The following section reviews the known ocular surface impacts of bisphenol-A and phthalates.

3.3.1.1 Bisphenol-A

Bisphenol A is a chemical compound used in the production of plastics, including food and drink containers. It is one of the most studied endocrine-disrupting chemicals in the context of health. It has the ability to bind to estrogen receptors, but has been estimated to have only a 1/1000th to 1/10,000th of the binding affinity of natural estradiol [148]. In an *in vitro* study looking at monocyte-derived dendritic cells of patients with primary Sjögren syndrome, exposure to bisphenol A increased expression of estrogen receptor- α and altered the function of these cells, including inducing a higher expression of interferon- γ and interleukin-17 mRNA

in T-cells. The authors suggested that bisphenol A exposure could accelerate the development and deterioration in function of primary Sjögren syndrome [149].

In a small case-control study (n = 33 dry eye, n = 21 controls), significant positive correlations were found between dry eye disease signs and several endocrine-disrupting chemicals in the urine, including methylparaben, ethylparaben, methyl-protocatechuic acid and triclocarban [150]. However, no association with bisphenol A or S was found. Also, no clear difference arising from the consumption of liquids from plastic bottles or canned food was found between dry eye patients and controls, which may indicate that either these compounds are widely distributed or that the limited sample size hampered any strong conclusions being drawn [150].

3.3.1.2 Phthalates

Phthalates are esters of phthalic acid. They are often used to increase the flexibility and durability of polymer plastic matrices and are found in cosmetics (see the TFOS Lifestyle Impact of Cosmetics Report [151]), children's items, plastics and food storage materials. Humans are exposed via foods that have contacted products containing phthalates or via air-borne contamination. No studies on dietary phthalate intake and ocular surface disease have been conducted to date, but exposure to air-borne phthalates has been associated with mucous membrane irritation, including ocular symptoms [26].

3.3.2 Mercury

Mercury is a heavy metal that, even in small amounts, can be extremely toxic to humans. Teratogenicity and neurotoxicity, including to the retina and optic nerve, are important adverse effects, but also immunotoxic effects have been shown [27]. The most common route of mercury poisoning is consumption of mercury-contaminated seafood [145].

In a cross-sectional study of 22 male metal manufacturing plant workers who had systemic mercury intoxication, ocular surface symptoms were frequent [152]. Specifically, increased

tear osmolarity, altered tear cytokine tear levels, altered corneal sensitivity and disrupted subbasal corneal nerve morphology were found [152]. In two independent Korean population-based studies, blood concentrations of mercury were linked to dry eye symptoms [153, 154]. In a sample of 4,761 adults, those with dry eye symptoms more often had blood mercury levels exceeding the median levels than those without dry eye symptoms (51.7% versus 45.7%, $p = 0.02$) [153]. In 23,376 participants, mercury blood concentrations were significantly associated with the presence of persistent dry eye symptoms (odds ratio: 1.39 (CI: 1.02-1.89) for persons in the third versus the first tertile of blood mercury concentration [154]. Although the source of intoxication was not defined, the authors stated that the main source of mercury was likely to be fish or shell-fish consumption [154]. In data analyzed from 6,587 adults, environmental exposure to lead and mercury was found to be related to the development of pterygium (odds ratio 2.22 (CI: 1.30, 3.78) and 1.64 (CI: 1.04, 2.59), respectively [155]. Several pathophysiological hypotheses have been proposed by the authors of these studies: first, neurotoxicity of the autonomous nervous system leading to decreased lacrimal gland function; second, accumulation of mercury in the conjunctiva and acceleration of free radical reactions leading to inflammation of the ocular surface epithelium; and third, increased plasma osmolarity leading to increased tear hyperosmolarity [153, 154].

3.3.3 Alcohol

Two small interventional studies have investigated the effect of a single event of alcohol intake on several ocular surface parameters, and found increased tear osmolarity, shortened TBUT and more ocular pain in the hours after alcohol consumption (0.75 g/kg ethanol or 200 mL 25% vodka) [156, 157]. Alcohol was detectable in the tear film two hours after intake, but not after eight hours [156]. A meta-analysis that included 10 studies (9 case-control and 1 cross-sectional) found that alcohol was weakly associated with dry eye disease. No clear increased risk of dry eye was seen in heavy drinkers and the authors attributed this to a possible protective

effect of neuropathy on symptoms associated with heavy drinking [158]. There was large heterogeneity between studies including the assessment of alcohol intake and dry eye, and none of them was primarily designed to assess the effect of alcohol use.

A large population-based study in the Netherlands ($n = 77,145$) found alcohol use in females to be associated with an increased risk of dryness symptoms compared to no alcohol use, but increasing alcohol use was protective in males. The authors emphasized the possible sex-specific effects of alcohol on the ocular surface, with a complex underlying interplay between hormonal changes, corneal neuropathy and sensitivity, central nervous system changes, inflammation on the ocular surface and dry eye parameters [159].

Alcohol use has not been linked to allergic eye disease in studies to-date, but there is evidence that its consumption can trigger allergy and promote hypersensitivity to different allergens [160]. Alcohol use has also been shown to impact the efficacy and safety of oral H1-antihistamine use [161]. Further longitudinal studies are needed to elucidate the short- and long-term effects of alcohol use at the ocular surface. The effects of alcohol on the ocular surface are discussed in greater detail in the TFOS Lifestyle Impacts Report [162].

3.3.4 Food additives and non-nutritional chemicals

There has not yet been any published research related to the possible effects of food additives and non-nutritional chemicals, such as nanoparticles, emulsifiers and flavor enhancers including glutaminase and monosodium glutamate, on the ocular surface. These compounds have been increasingly associated with various negative health effects in the human body [163-165]. Future studies should examine whether they have a role in ocular surface disease.

3.4 Dietary supplements

The previous section highlighted the evidence regarding the impact of individual nutritional elements within the diet on the ocular surface. This is notoriously difficult to study, except in cases of clear dietary deficiency or excess. The following section therefore focuses on dietary supplementation.

Dietary supplements are products taken orally that contain an ingredient that intends to supplement the diet. They may contain vitamins, minerals, fiber, amino acids, essential fatty acids, herbs, botanicals, enzymes or other substances. Common forms are tablets, capsules, powders, liquids and bars [152]. Being a portmanteau (combination of the words) from “nutrition” and “pharmaceuticals,” “nutraceuticals” are a sector of dietary supplements with products derived from food sources that intend to provide health benefits in addition to their normal nutritional values. The definitions and regulatory control of dietary supplements and nutraceuticals differ between countries.

3.4.1 Caffeine

In an examiner-masked placebo-controlled study with 41 healthy volunteers, caffeine, 5 mg/kg body weight dissolved in 200 mL water, increased Schirmer scores significantly from baseline and compared to placebo (200 mL water only). This effect was seen in the first 90 minutes after ingestion and disappeared thereafter [138]. In another double-masked placebo-controlled study involving 78 healthy volunteers who abstained from caffeine use for at least 6 days, pure caffeine capsules (5-7 mg/kg body weight) increased tear meniscus height by an average of 0.08 mm after 60 minutes compared to placebo [166]. There were also associations between certain genetic polymorphisms in the adenosine A2a receptor and cytochrome P450 1A2 genes and the increase in tear meniscus height. No trials have been performed in patients with dry eye disease, nor have there been long-term studies, which are needed to elucidate caffeine as a possible management option.

In a large population-based study involving 85,302 participants, caffeine use (calculated from coffee, tea, cola and energy drinks) was associated with a protective effect on dry eye (odds ratio: 0.971 (CI 0.96-0.99) per 100 mg/day), but this protective effect was not seen after correction for dry eye-associated comorbidities [167]. Similarly, in a Korean population-based study of 9,752 adults, prevalence of dry eye decreased with increasing coffee consumption, but the apparent protective effect did not remain after correction for age and sex [168]. In a smaller study in New Zealand community residents (n = 322) increased caffeine consumption was a borderline significant protective factor for dry eye [as defined by the Tear Film and Ocular Surface Dry Eye Workshop II (TFOS DEWS II) criteria, odds ratio 0.82 (CI: 0.68-0.99) per serving per day] in a multivariate model investigating multiple modifiable lifestyle factors [169]. Other smaller population-based studies in the past have shown no clear association with prevalence and incidence of dry eye [169-174], with the exception of one prevalence study where a significant protective effect was found for caffeine users [175]. Therefore, based on the current evidence, caffeine (which does not cause fluid loss in excess of the volume ingested despite its mild diuretic effect) does not appear to be a risk factor of dry eye disease and may have beneficial effects on tear production and symptoms, but further research is needed to verify the findings.

A small trial in low caffeine consumers showed that caffeine intake (capsule of 4 mg/kg body weight) reduced corneal deformability and increased intraocular pressure values, implying that exogenous factors are also important to consider in the diagnosis and management of disorders characterized by changes in the biomechanical properties of the cornea [176]. The effects of caffeine on the ocular surface including mechanisms of action are further discussed in the TFOS Lifestyle Impacts Report [162].

3.4.2 Collagen

Collagen is the most abundant structural protein in various connective tissues, including the skin, bone, sclera, and cornea. It is the target in riboflavin-mediated cross-linking to retard the progression of keratoconus. Collagen-based dietary supplements, which are extracted from animal sources, are used mainly in the field of dermatology with some evidence for improved wound healing and increased skin health such as wrinkle reduction and skin hydration [177-179]. In addition, they may help recovery after joint injury and reduce symptoms in osteoarthritis [180, 181]. So far, no studies have been performed to investigate the effect of dietary collagen supplementation or its amino acids glycine and proline and precursor ornithine on ocular surface health or wound healing.

3.4.3 Herbs

The term 'herb' usually refers to leaves and stems of soft-stemmed plants that grow in temperate climates [182]. *Tripterygium* glycosides extracted from *Tripterygium wilfordii* Hook *F* have been reported to have a therapeutic effect on Graves ophthalmopathy [183]. There is no systematic review or meta-analysis of herbs for eye symptoms caused by thyroid dysfunction, but there is one ongoing randomized controlled trial in which pingmu decoction, a Chinese balm containing multiple herbs, is being examined for Graves ophthalmopathy [184]. Oral ingestion of multiple Chinese herbs have been reported to be effective against dry eye disease development in clinical studies including randomized controlled trials [185-187]. In a randomized, double-masked, controlled trial of 80 individuals with dry eye disease between topical eye drops and the Chinese Herb, Chi-Ju-Di-Huang-Wan, or the topical eye drop with a placebo rose Bengal staining improved by two weeks and TBUT improved by four weeks [185]. In a randomized, unmasked, controlled trial of 60 individuals with both diabetes and dry eye disease, between the control (Western medicine treatment: artificial tears without preservatives used six times a day) or experimental treatment (combined treatment of traditional Chinese medicine of Qiwei Baizhu powder, Zhibai Dihuang, and Liuwei Dihuang,

and Western medicine) the experimental group showed an improved TBUT, a reduction in corneal staining and reduced inflammatory mediators in the tear film, including interleukin-1, -8 and tumor necrosis factor- α [186]. In a double-masked, randomized controlled trial of 50 individuals with diabetes, between traditional Chinese herbal medicine goshajinkigan orally, 7.5 g/day for 3 months, or a placebo of 6.0 g/day for 3 months; a third group of 25 individuals without diabetes received the goshajinkigan orally, 7.5 g/day for 3 months [187]. The group with diabetes that was treated with goshajinkigan showed an improvement in corneal sensitivity, Schirmer score and corneal staining, while the other two groups did not change [187]. In conclusion, whilst there is some evidence for effects of certain herbal combinations on the ocular surface, further research using appropriate clinical designs and other herbal combinations are needed to draw firm conclusions about the potential benefits of individual herbs or herbal mixtures.

3.4.4 Honey

There is evidence that honey can have antibacterial, antifungal, antiviral, anti-inflammatory and anti-oxidative properties, and may aid in the healing of wounds [188]. Several randomized clinical trials have investigated the effect of topically applied Manuka honey (*Leptospermum* spp.) in and around the eye, providing evidence of improvements in tear film evaporation, meibomian gland dysfunction (MGD), blepharitis, eyelid wound healing, corneal ulcers and vernal conjunctivitis [189-197].

The effect of honey as a dietary supplement on ocular surface disease has been less well studied. One double-masked randomized controlled trial investigated the effect of oral royal jelly, a gelatinous substance produced by bees, (6 x 1200 mg tablet daily) for 8 weeks versus placebo in 41 patients with dry eye disease. TBUT and Schirmer scores improved significantly in the royal jelly group, with Schirmer scores significantly better compared to placebo only in patients with a baseline score below 10 mm. No clear improvements were found for dry eye

symptoms [198]. A randomized controlled trial investigating the effect of three types of dietary honey on allergic rhinoconjunctivitis in addition to standard care found that none of the honey groups improved symptoms compared to placebo [199]. A randomized controlled pilot study found that addition of dietary birch-pollen honey significantly reduced allergic symptoms compared to controls (conventional medications only), including conjunctival symptoms [200]. Further studies should clarify if there is a role for oral honey in the management of ocular surface disease.

3.4.5 Minerals

With regard to dry eye disease, several clinical trials have investigated supplementation with a combination of minerals, vitamins, anti-oxidants and/or omega-3-fatty acids [201-204], but none has examined the role of minerals alone. Oral lactoferrin supplementation for one month in 10 patients with dry eye disease secondary to Sjögren syndrome was reported to improve dry eye symptoms [205]. Lactoferrin containing selenium instead of iron has been found to be incorporated into the epithelial cells of the cornea, thereby decreasing oxidative injury in an animal model of dry eye disease [206].

There is evidence of an increased prevalence of autoimmune thyroid disease and Graves' ophthalmopathy in persons with low dietary selenium intake (below 70 $\mu\text{g/L}$) [207, 208]. A meta-analysis of two trials ($n = 197$) evaluating the efficacy of selenium supplementation (200 $\mu\text{g/day}$) for 6-9 months in patients with non-severe Graves' ophthalmopathy having standard therapy found no statistically significant difference in thyroid stimulating hormone receptor antibodies or thyroid peroxidase antibody titers compared to placebo [209]. Similarly, another review concluded that, although commonly prescribed [210], the evidence does not yet support a role for selenium supplementation in standard care of auto-immune thyroiditis, with a possible exception for persons with a known selenium deficiency [208].

3.4.6 Omega-3 and -6

The omega-3 and omega-6 polyunsaturated fatty acids are the most extensively studied dietary supplements in ocular surface disease, with numerous randomized controlled trials, systematic reviews and meta-analyses, mostly in patients with dry eye disease or MGD.

3.4.6.1 Dry eye and MGD

3.4.6.1.1 Overview of randomized controlled trials

Table 1 (omega-3 only) and Table 2 (omega-3 and -6 combined) summarize the randomized controlled trials that have investigated the role of omega-3 fatty acid supplementation on dry eye disease or MGD. Differing daily doses, subtypes (omega-3: eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid; omega-6: γ -linolenic acid, linoleic acid; and a form of omega-3: triglyceride, phospholipid, ethyl-ester, or re-esterified) and sources (flaxseed oil, krill oil, fish oil, sea buckthorn oil, borage oil, black currant seed oil) of omega fatty acids have been investigated across studies. Also, study duration (30 days to one year), sub-type of dry eye, comparators (olive oil, corn oil, sunflower oil, wheatgerm oil, safflower oil, middle chain triglycerides, none) and exclusion of other eye treatments have differed between studies. Only one study compared three interventions (fish oil vs krill oil vs placebo) [77].

Table 1: Overview of randomized clinical trials of oral omega 3 supplementation for dry eye

Study (author, year)	Type of dry eye	Intervention (daily dose)	Comparator (daily dose when applicable)	Duration	Parameters with significant improvement to comparator (including effect size if available)	Parameters without significant improvement to comparator (including effect size if available)
DREAM study group, 2018 [8]	DED (both symptoms and signs)	2000mg EPA + 1000mg DHA (n=349)	5000mg refined olive oil (n=186)	12 months	None	-OSDI score (-13.9 vs -12.5) -Conjunctival staining score (-0.4 vs -0.4) -Corneal staining score (-0.6 vs -0.7)

Study (author, year)	Type of dry eye	Intervention (daily dose)	Comparator (daily dose when applicable)	Duration	Parameters with significant improvement to comparator (including effect size if available)	Parameters without significant improvement to comparator (including effect size if available)
						-TBUT (+0.7 vs +0.6) -Schirmer score (+0.4 vs +0.3)
Park et al, 2021 [211]	Dry eye symptoms 1 month after cataract surgery	1680mg EPA + 506 mg DHA (re-esterified) + artificial tears 4x/ day (n=32)	Artificial tears 4x/ day only (n=34)	8 weeks	-Oxford staining score (-0.63 vs -0.14) -OSDI score (-6.22 vs +1.58) -DEQ score (-3.78 vs -0.36) -MMP-9 level decrease (9/32 vs 4/34)	-TBUT (+0.41 vs -0.09) -Schirmer score (+2.54 vs +0.57)
Jo et al, 2021 [212]	Mild to moderate DED and MGD (signs and symptoms)	600 mg EPA + 1640mg DHA (n=24)	3000 mg olive oil (n=26)	8 weeks	-TBUT (+1.87 vs +1.33) -MGD score (-1.5 vs -0.5)	-Corneal staining score (-2.6 vs -1.6) -OSDI score (-2.5 vs -2.0) -SM tube test (-0.3 vs +0.3)
Macasai, 2008 [213]	Moderate to severe chronic blepharitis and obstructive MGD	Flaxseed oil capsules 6000 mg (n=17)	Olive oil capsules (n=20)	1 year	- Telangiectasias (-1.1 vs -0.3)	-OSDI score (-11.6 vs -7.1) -TBUT (+4.7 vs +3.9) -Schirmer score (+1.8 vs +2.2) -Fluorescein staining (+0.8 vs -0.9) Rose Bengal staining (-1.1 vs -1.4) -Collarettes (-0.7 vs -0.6) Scurf (0.0 vs -0.1) -Dystichiasis -Madarosis
Bhargava et al, 2013 [214]	Both DED and MGD (symptoms and signs)	650mg EPA + 350mg DHA (n=264)	Corn oil (n=254)	3 months	-Symptom score value (-2.02 vs -0.48) - Schirmer score (+0.62 vs +0.14) -TBUT (+2.54 vs +0.13)	-Rose Bengal scores (not directly compared) -Conjunctival impression cytology (not directly compared)
Bhargava et al, 2015 [80]	Computer users (>3h/day) with dry eye symptoms	360mg EPA + 240 mg DHA (n=220)	Olive oil (n=236)	3 months	-symptom score (-4.1 vs -0.7) -Schirmer score (+1.2 vs +0.6) -TBUT (+3.3 vs +1.4) -Nelson grade (-0.7 vs -0.1)	None
Bhargava et al, 2016 [215]	VDT users with dry eye symptoms	720 mg EPA + 480 mg DHA (n=256)	Olive oil (n=266)	45 days	- Symptom score	- TBUT -Nelson grade -Schirmer score
Bhargava et al, 2015 [76]	Female contact lens users with dry eye symptoms and lens wear discomfort	720 mg EPA + 480 mg DHA (n=240)	Corn oil (n=256)	6 months	-Symptom score (-4.7 vs -0.5)	-TBUT (+3.3 vs +0.3) -Nelson grade (-0.7 vs -0.1) -Schirmer score (+2.1 vs +0.2)
Bhargava et al, 2016 [216]	Rosacea patients with dry eye symptoms	360mg EPA + 240 mg DHA (n=65)	Olive oil (n=65)	6 months		-Symptom score (-5.3 vs -0.2) - Meibomian gland score (-1.3 vs 0.0) -TBUT (+3.1 vs -0.2) - Schirmer score (+1.4 vs -0.3)
Malhotra et al, 2015 [217]	Moderate MGD	720 mg EPA + 480 mg DHA + warm	Warm compresses, lid massage,	12 weeks	-OSDI score (-25.4 vs -9.0)	-Rose bengal staining score (-1.6 vs -1.4)

Study (author, year)	Type of dry eye	Intervention (daily dose)	Comparator (daily dose when applicable)	Duration	Parameters with significant improvement to comparator (including effect size if available)	Parameters without significant improvement to comparator (including effect size if available)
	(symptoms and signs)	compresses, lid massage, artificial tears (n=30)	artificial tears only (n=30)		- TBUT (+5.2 vs +2.5) - Ocular protection index (+1.0 vs +0.5) - Fluorescein staining score (-3.1 vs -2.1) - Meibum expressibility (-0.8 vs -0.3) - Meibum quality (-7.1 vs -1.7) - Contrast sensitivity (several photopic and mesopic variables)	-Schirmer score (-0.8 vs 0.0)
Kawakita et al, 2013 [218]	Dry eye (symptoms and signs)	Fish oil (1245mg EPA, 540 mg DHA) (n=15)	Mainly middle chain triglycerides (n=12)	12 weeks	- Symptom score -TBUT -Rose bengal staining	-Schirmer score -Fluorescein staining
Kangari et al, 2013 [219]	Dry eye disease (symptoms)	360mg EPA + 240 mg DHA (n=33)	Middle-chain triglycerides (n=31)	30 days	-OSDI-score (-26% vs -4%) -TBUT (71% vs 3.3% improvement) -Schirmer score (22.3% vs 5.1% improvement)	None
Deinema et al, 2017 [77]	Mild to moderate DED (signs and symptoms)	Fish oil (1000mg EPA + 500mg DHA) (n=19) or Krill oil (945mg EPA + 510 DHA) (n=18)	Olive oil (1500 mg) (n=17)	3 months	-Tear osmolarity for both fish oil and krill oil (-19.8 vs -18.6 vs -1.5) -OSDI for krill oil only (-18.6 vs -10.5) -TBUT - Ocular redness for both fish oil and krill oil (-0.3 vs -0.5 vs +0.2) - Tear IL-17A level for krill oil only (-27.1 vs +46.5)	-NIBUT -Ocular Surface staining - Tear volume (TMH) -Schirmer score -Anterior blepharitis degree -MG capping degree -Tear IL-2, IL-4, IL-6, IL-10, IFN- γ , TNF α levels
Epitropoulos et al, 2016 [220]	DED diagnosis with MGD stage 1 or 2 (mild to moderate)	1680 mg EPA + 560 mg DHA (n=54)	3136mg lonoleic acid (n=51)	12 weeks	-OSDI score (-17.0 vs -5.0) - Tear osmolarity (-19.4 vs -8.3) - TBUT (+3.5 vs +1.2) - MMP-9 positivity (-67.9% vs -35.0%)	-Oxford corneal staining (-0.6 vs -0.6) -MGD stage (-0.3 vs -0.4) -Schirmer score (+1.6 vs +1.3)

DED = dry eye disease; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid; IL = interleukin; IFN = interferon; MG = meibomian gland; MGD = meibomian gland dysfunction; MMP = matrix metalloproteinase; NIBUT = non-invasive breakup time; OSDI = Ocular Surface Disease Index; SANDE = Symptom Assessment in Dry Eye questionnaire; TBUT = tear breakup time; TFOS DEWS = Tear Film and Ocular Surface society Dry Eye Workshop; TNF = tumor necrosis factor.

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Table 2: Overview of randomized clinical trials of combined oral omega 3 and 6 supplementation for dry eye

Study (author, year)	Type of dry eye	Oral omega-3 /6 intervention (daily dose)	Comparator	Duration	Parameters with significant improvement to comparator (including effect size)	Parameters without significant improvement to comparator (including effect size)
Larmo et al, 2010 [221]	DED (symptoms)	2g sea buckthorn oil (n=45)	2g placebo oil (n=41)	3 months	-Tear osmolarity (+8 vs +12)	-TBUT (0 vs +1) -Schirmer score (0 vs 0) -OSDI score (-5 vs -4) - 'Significant improvement' of tear osmolarity compared to placebo, but still an increase in dry eye (tear osmolarity went up in both groups).
Brignole – Baudouin et al, 2011 [202]	Mild to moderate DED (signs and symptoms)	Fish oil (427.5mg EPA + 285mg DHA) + 15mg borage oil (omega 6 source) + several other vitamins/antioxidants (n=61)	575mg medium-chain triglycerides (n=66)	3 months	-HLA-DR positive cells % (-8.10 vs -0.06)	-Symptom score (-2.6 vs -1.8) -Schirmer score (+0.5 vs +0.4) -BUT (+0.5 vs +0.4) -Fluorescein staining (-0.7 vs -0.5) -Lissamine staining (-1.4 vs -0.9)
Sheppard et al, 2013 [222]	Moderate and severe DED, postmenopausal women	196mg ALA + 126mg EPA + 99mg DHA + 39mg DPA + 710mg LA + 240mg GLA + <3 mg ARA + several vitamins and magnesium (n=19)	Sunflower oil (n=19)	24 weeks	-OSDI scores -HLA-DR expression -CD11c-positive dendritic cells -Corneal surface asymmetry index	-Corneal surface regularity index -Schirmer score -TBUT -Fluorescein and lissamine green staining -Lid margin erythema -Chemosis -Adjunctive artificial tear use
Ng et al, 2021 [223]	Moderate to severe DED (TFOS DEWS II criteria: both symptoms and signs)	1200mg EPA + 300mg DHA + 150mg GLA (n=24)	Coconut and olive pomace oil (n=26)	3 months	None	-OSDI score -SANDE score -Schirmer score -NIBUT (and many other 2 nd outcome variables)

ALA = alpha-linolenic acid; ARA = arachidonic acid; CD11c = cluster of differentiation 11c; DED = dry eye disease; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid; GLA = gamma-linolenic acid; HLA-DR = human leukocyte antigen D-related; LA = linolenic acid; MMP = matrix metalloproteinase; OSDI = Ocular Surface Disease Index; TBUT = tear breakup time.

3.4.6.1.2 *Conclusions of published systematic reviews and meta-analyses*

Meta-analyses in dry eye disease have been published on this topic since 2014 [9, 15-18]. One of the three most recent meta-analyses was a Cochrane systematic review on the role of omega-3 and omega-6 fatty acids for dry eye disease [9]. It included a total of 34 randomized controlled trials with 4314 adult participants from 13 countries with several subtypes and severities of dry eye, and with follow-up ranging from 1 to 12 months [9]. Several comparisons were made, and the main conclusions were as follows:

- (1) Low certainty evidence was found for a reduction in dryness symptoms for oral long-chain omega-3 versus placebo. Moderate certainty evidence was found for a probable benefit in increasing aqueous tear production relative to placebo, but this increase was judged to be not clinically meaningful.
- (2) Moderate certainty evidence was found for no effect of oral combined omega-3 and omega-6 versus placebo for Schirmer score, and moderate certainty was found for a probable improvement in TBUT. Effects on symptoms, ocular surface staining and tear osmolarity were unclear because of insufficient data or extensive heterogeneity precluding meta-analysis.
- (3) Low certainty evidence was found for reduction of symptoms with oral omega 3 plus conventional therapy versus conventional therapy alone. Data for other dry eye outcomes could not be combined.
- (4) Moderate certainty evidence was found for a probable improvement in dryness symptoms for oral long-chain omega-3 versus omega-6. Low certainty evidence was found for a potential improvement in tear osmolarity. Effects on other dry eye outcomes could not be meta-analyzed.

In addition, for oral flaxseed oil (short chain omega-3) versus placebo (two randomized controlled trials), and omega-6 versus placebo (six randomized controlled trials) results could not be meta-analyzed. Of the six trials [224-229] that investigated the effect of oral omega-6 fatty acids (with either γ -linolenic acid (GLA) or a combination of linoleic acid (LA) and GLA),

only one study [224] reported a greater improvement of dry eye symptoms compared to placebo.

Overall, the authors concluded that there is a possible role for long-chain omega-3 supplementation in dry eye disease, with effects more likely for clinical signs than for symptoms, but evidence was judged uncertain and inconsistent. The authors also noted that the effect of omega-3 fatty acids on symptoms was not significant when a placebo supplement was used as comparator, but was significant when omega-6 supplementation (e.g. corn and safflower oil) was used as the comparator, suggesting a possible important role for the relative ratio of omega-3 to omega-6 consumption [9]. This may also suggest that omega-6 does not serve well as a control. The authors also judged none of the 34 included studies to have a low risk of bias in all seven possible domains.

Another meta-analysis investigated possible benefits of omega-3 versus placebo and included 17 randomized controlled trials with a total 3,363 patients. The authors reported that omega-3 supplementation decreased dry eye symptoms, and improved corneal fluorescein staining, TBUT and Schirmer scores compared to placebo [16]. A reason for the different findings with respect to symptom improvement compared to the previous Cochrane review, was that the Cochrane review meta-analyzed only studies that included the Ocular Surface Disease Index (OSDI) symptom score, while the other meta-analysis also included studies that utilized other symptom questionnaires. Also, the meta-analysis included studies investigating short-chain omega-3-polyunsaturated fatty acids (from flaxseed oil) in addition to long-chain omega-3 polyunsaturated fatty acids, and the authors did not undertake separate investigations for placebos/comparators with or without omega-6. In a meta-regression analysis, the authors found a greater improvement of symptoms and TBUT with omega-3 in studies performed in India. The authors speculate that omega-3 fatty acid dietary intake in India may be lower due to a predominantly vegetarian diet, indicating a role of baseline omega-3 values in the amount

of treatment effect [16]. No relationship between efficacy and the dose or duration of omega-3 treatment was found [16].

Another meta-analysis of 13 randomized controlled trials found that patients who received fatty acids (both omega-3 and combined omega-3 and omega-6) treatment without other eye medications showed greater improvement than placebo in TBUT, Schirmer scores, tear osmolarity and OSDI scores [15]. This improvement was not observed or was observed to a lesser degree in those who used supplemental fatty acids concurrent with other eye treatments. The authors also found that this positive effect weakened with treatment duration for TBUT and OSDI [15].

3.4.6.1.3 Results of individual primary research studies

The Dry Eye Assessment and Management trial, the largest randomized clinical trial to-date on the effect of omega-3 fatty acids [8], involved a total of 349 dry eye patients who were assigned to receive fish-derived omega-3 (2000 mg eicosapentaenoic acid plus 1000 mg docosahexaenoic acid/day) for 12 months, and 186 patients to receive placebo (olive oil). Mean change of the primary outcome variable OSDI symptom score was not significantly different between groups (-13.9 vs -12.5, $p = 0.21$). Also, no significant differences were seen between groups in the secondary outcomes of corneal and conjunctival staining scores, TBUT and Schirmer scores. In addition, an extension study showed that those who had received omega-3 supplements for 12 months and stopped these did not have significantly worse outcomes than those who continued omega-3 supplements for an additional 12 months [78]. A study looking at additional outcome variables did find a significant improvement compared to placebo for tear osmolarity ($p = 0.02$), however the authors questioned the clinical significance of lowered osmolarity. No differences between groups for matrix metalloproteinase-9 levels, tear meniscus height, bulbar conjunctival redness or meibomian gland dropout were found [230]. Another add-on study demonstrated no clear or consistent changes in ocular inflammatory

status as measured by the frequency of HLA-DR-expressing conjunctival cells and tear cytokines (interleukins-1 β , -6, -8, -10, -17A, interferon- γ , tumor necrosis factor- α) between groups [231]. It should be noted that the previously described Cochrane review [9] did include the results of the Dry Eye Assessment and Management study in their analyses [231]. A significant shortcoming of the Dry Eye Assessment and Management trial is that the authors evaluated only one eye, making it difficult to account for the known heteroscedasticity of dry eye disease.

Since the meta-analyses, several new randomized controlled trials have been published on the effects of omega-3 and omega-6 fatty acids on dry eye-related phenotypes. An investigation of the effect of omega-3 fatty acids in addition to a soft silicone plug in the inferior punctum in non-dry eye patients who had used systemic isotretinoin therapy for at least four months found no significant improvements in OSDI, TBUT, tear osmolarity, Schirmer scores, ocular surface staining score for the group that received additional omega-3 fatty acids compared to the punctal plug only group. Meibum quality, however, was significantly better in the group with omega-3 [232].

A randomized controlled trial using a re-esterified triglyceride form of omega-3 fatty acids (1680 mg eicosapentaenoic acid and 506 mg docosahexaenoic acid/day for eight weeks), which may have higher bioavailability than the ethyl ester form, found a reduction in ocular surface inflammation (matrix metalloproteinase-9), Oxford staining and symptoms scores compared to placebo. These changes occurred in a setting of new-onset dry eye, one month after uncomplicated cataract surgery, indicating a possible role for omega-3 fatty acids in surgically-induced dry eye [211].

A study of a daily oral supplement containing both omega-3 and omega-6 fatty acids (1200 mg eicosapentaenoic acid, 300 mg docosahexaenoic acid, and 150 mg γ -linoleic acid) for three months versus placebo (coconut and olive oil) in 50 patients with moderate-to-severe dry eye

disease found no differences between groups in any of the ocular outcome variables (OSDI score, Symptom Assessment Questionnaire iN Dry Eye (SANDE)-score, TBUT, tear meniscus height, tear osmolarity, ocular surface staining, Schirmer score or meibography). A post hoc subgroup analysis did find a significant improvement in dryness symptoms compared to placebo, however, in highly symptomatic patients (OSDI-score > 52, n = 25) [223].

A randomized controlled trial in 24 patients with mild-to-moderate dry eye disease with MGD evaluated a formulation with 600 mg eicosapentaenoic acid and 1640 mg docosahexaenoic acid and compared this with placebo containing 3000 mg of olive oil. Borderline significant improvements in TBUT and MGD scores were observed compared to placebo, while an improvement was not apparent for corneal staining, OSDI score, and strip meniscometry [212].

A recent study investigated whether supplementation of marine omega-3 fatty acids (1 g daily) and vitamin D₃ (2,000 IU daily) prevented onset of dry eye disease in healthy adults, as an ancillary study within the vitamin D and omega-3 trial (VITAL) that investigated the prevention of cancer and cardiovascular disease [233]. In 23,523 adults aged 50 years and over, who were free of a diagnosis of dry eye disease at study entry, supplementation over 5.3 years (range 3.8-61 years) did not reduce the incidence of dry eye disease (with or without incidence of severe dry eye symptoms) [233].

3.4.6.1.4 Other oils as comparators

Oils including olive, corn, and safflower oil have been used as oral comparators in several of the omega fatty acid trials on dry eye. Corn oil and safflower oil contain omega-6 fatty acids, which may be pro-inflammatory [234] and may have an adverse effect on dry eye. This in turn may enhance the chance of finding a difference with omega-3 fatty acid intervention in trials [9]. Olive oil contains oleic acid and polyphenols (particularly extra virgin olive oil) which have been shown to have anti-inflammatory and anti-oxidative properties [235, 236], although

any effect on the ocular surface is currently unknown. It may be that oils, excluding polyunsaturated fatty acids, may have a beneficial effect on the ocular surface and may not act as a true placebo in these studies. Also, the Mediterranean diet, which is rich in olive oil but also includes other potential healthy elements, may be protective of dry eye (see section 3.8.1.2).

3.4.6.2 Corneal neuroprotection

A pilot randomized controlled trial with 12 dry eye participants found that daily omega-3 fatty acids (1000 mg eicosapentaenoic acid + 500 mg docosahexaenoic acid) for 90 days significantly increased corneal nerve branch density and corneal nerve fiber length compared to placebo, indicating neuroprotective effects in the corneal sub-basal plexus [81]. A larger double-masked randomized controlled trial investigated the effects of oral omega-3 supplementation versus placebo on corneal nerve fibers in 43 patients with type 1 diabetes. Central corneal nerve fiber length increased significantly more with oral omega-3 than with placebo at day 180, again indicating a role of omega-3 in modulating peripheral nerve health [237]. A meta-analysis of omega-3 supplements for improving peripheral nerve health found low certainty evidence of a reduced incidence of peripheral neuropathy and a preservation of sensory nerve action potential amplitude compared to placebo in individuals receiving chemotherapy, but concluded evidence is too limited to extrapolate the findings to predict benefits in other conditions characterized by peripheral nerve damage [238]. Future studies with adequate statistical power are needed to elucidate any neuroprotective effects of omega-3 fatty acids at the ocular surface [20].

3.4.6.3 Allergic eye disease

Although a meta-analysis found evidence for benefits of increased omega-3 fatty acids in the maternal diet in the prevention of childhood allergic disease, including atopic eczema, food sensitization and positive skin prick tests [19], no trials on allergic eye disease have been

reported in humans. A protective effect of a diet rich in omega-3 fatty acids on ragweed pollen-induced allergic conjunctivitis in mice was found in one study [239]. T helper 2 immune responses and total serum immunoglobulin E levels were not affected, but levels of omega-6-derived proinflammatory lipid mediators in the conjunctiva were markedly reduced in these mice [239], indicating a role of lipid mediators and omega-3 fatty acids in allergic conjunctivitis [240]. Further studies, and particularly human studies, are needed to confirm any role for omega 3 fatty acids in the treatment of allergic conjunctivitis.

3.4.6.4 Safety

All meta-analyses discussed concluded that polyunsaturated fatty acids have relatively few adverse events, but only about half of randomized controlled trials contained a report on the presence or absence of adverse effects [9]. Similarly, a meta-analysis on the effects of omega-3 fatty acids on eye health (but not including any ocular surface disease) concluded that intake was associated with few minor, mostly gastrointestinal, side-effects, but also noted that studies often do not report minor issues, and that more studies were needed to assess their safety [14]. Caution should be taken when polyunsaturated fatty acid supplementation is prescribed to patients with blood clotting disorders as omega-3 fatty acids have the potential to reduce platelet activity, although convincing evidence of increased risk of bleeding after supplementation is lacking [241, 242]. Indeed, patients with cardiovascular disease taking high dose fish oil combined with both aspirin and clopidogrel showed no increased risk of bleeding compared to patients on aspirin and clopidogrel alone [243]. Similarly, fish oil supplementation did not increase perioperative bleeding and actually reduced the number of blood transfusions in 1,516 patients post-cardiac surgery [244]. A meta-analysis of 52 publications (32 of these being on healthy participants and 20 on patients undergoing surgery) confirmed these findings and found no increased risk of bleeding during or after surgery, despite the finding of reduced platelet aggregation in healthy participants [245]. Other diseases where precaution has been

advised are liver disease and atrial fibrillation [75]. Omega-3 serum levels in men have also been linked with an increased risk of prostate cancer [246]. None of these safety precautions or side-effects have high-level evidence. Indeed, the European Food Safety Authorization concluded that long-term supplemental intakes of eicosapentaenoic acid and docosahexaenoic acid up to 5 g/day was not associated with bleeding complications or other safety concerns for adults [247]. The Food and Drug Administration of the USA recommends a daily intake of omega-3 of 500 mg/day, with no more than 3000 mg, with a maximum of 2000 mg from supplements [242].

3.4.6.5 Recommendations for treatment and future studies

Given the current possible efficacy and their relatively favorable safety profile, omega-3 fatty acids may be a relevant treatment option for patients with dry eye disease and MGD, acknowledging that their exact role in treatment remains incompletely understood. Indeed, a survey of optometrists in Australia and New Zealand found that eye care clinicians frequently prescribe oral omega-3 fatty acid supplements to their patients to manage both aqueous-deficient and evaporative dry eye disease [248]. The TFOS DEWS II report included the use of omega-3 fatty acids as one of several first step options in their staged dry eye disease management and treatment recommendations [75]. Another recommendation is that baseline measurements of omega-3 status are reported, potentially using surveys as a surrogate measure of blood levels of omega-3 fatty acids [249]. Future studies should determine if, and possibly which, dry eye patient subgroup(s) (subtype and/or severity of dry eye, or those who are omega-3 deficient) may benefit most from supplementation, whether a certain form or composition is preferable, what dosage and duration is best to recommend, and what dietary ratio of omega-3 to -6 is optimal for dry eye.

Assessment of dietary omega-3 intake needs to be qualified by the degree of successful endogenous conversion of α -linolenic acid (the parent of the omega-3 family) to long chain

fatty acids, for example [250]. A number of factors such as genetics, sex, age and dietary composition affect the process of conversion which is slow and inefficient. Consequently, a red blood cell measure of the degree of any omega-3/omega-6 imbalance (e.g., the Omega-3 Index [220]) could better guide therapeutic nutrition interventions and responses to them. The degree and rate at which omega-3 fatty acids are absorbed or made available at the site of physiological activity (bioavailability) may be independent of dietary intake [251].

Appropriate sample size calculation, prospective trial registration, provision of details regarding the polyunsaturated fatty acids intervention including form, and best practice dry eye diagnostic criteria to include participants are key recommendations from these studies [9].

3.4.7 Spices

Where herbs are derived from the leaves of a plant, spices are derived from the dried non-leafy parts such as seeds, roots, bark, buds, flowers and fruits [182]. It has been claimed that spices promote health, reduce mortality, and protect against the development of acute and chronic disease courtesy of their antioxidative, anti-inflammatory, anticarcinogenic, antimicrobial, and glucose- and cholesterol lowering activity. They may also favorably alter gut microbiota [252]. Research on the potential beneficial role of spices in ocular surface disease has been mostly focused on curcumin.

Curcumin is the principal curcuminoid of turmeric, a plant of the ginger family. It is an orange-yellow-colored polyphenol. Curcumin has been found to inhibit oxidative stress, angiogenesis and inflammatory processes in the human body and to help with restoring homeostasis [253-255]. Several in vitro and animal studies have found positive effects of topical curcumin agents in preventing corneal neovascularization [156, 256-258], promoting corneal wound healing [259], and inhibiting pathophysiological pathways of allergic conjunctivitis [260], pterygium [261, 262] and corneal endothelial dysfunction [263, 264].

Curcumin as a dietary source or food supplement has been less studied. A double-masked, randomized controlled trial with a supplement containing curcumin, lutein, zeaxanthin and vitamin D3 taken for 8 weeks showed significant improvements in ocular symptoms, Schirmer scores, TBUT and corneal staining scores compared to placebo in participants with mild-to-moderate dry eye [265]. Improvements in tear volume, TBUT, and tear inflammatory markers were also seen in an earlier study with the same supplement in rats, with benzalkonium chloride-induced dry eye [266]. Oral administration of both ultrasoluble curcumin and ultrasoluble turmeric showed reduced lymphadenopathy and salivary gland infiltrates and increased survival in mouse models of Sjögren syndrome and systemic lupus erythematosus [267]. In addition, in an *in vitro* study, curcumin has been shown to reduce mRNA expression as well as secretion of interleukin-6 by the salivary gland tissue from Sjögren patients [268]. Clearly, more research is needed to assess the potential beneficial role of dietary curcumin in both Sjögren syndrome and non-Sjögren syndrome dry eye.

3.4.8 Seeds

There is little evidence in humans about the therapeutic or prophylactic effects of plant seeds on ocular surface disease, with no systematic review or meta-analysis. Some seeds have been reported to be effective against ocular surface disease in clinical studies. For example, topical instillation of the polysaccharide from tamarind seed has been reported to improve dry eye symptoms, perhaps because the polysaccharide has a mucin-like structure [269, 270].

Further research is needed to determine the various effects of seed extracts on the ocular surface.

3.4.9 Vitamin supplementation

Deficiency in vitamins A or D and the impact on the ocular surface is discussed in section 3.1.2.1. Local ocular administration, oral administration, or systemic administration of vitamin

Vitamin A improves xerophthalmia symptoms [271-278]. Systemic vitamin A supplementation (oral or intramuscular) may reduce ocular surface abnormalities by goblet cell re-population of the conjunctiva and increasing their density, corneal re-epithelization and improved tear film quality [273, 279-281]. Short-term (3 days) oral (1,500 mg) vitamin A supplementation study on 30 male patients with dry eye compared to healthy age-matched men suggested that short-term oral vitamin A supplementation improves the quality of tears and not quantity in patients with dry eye [279].

The International Workshop on Meibomian Gland Dysfunction presented evidence that 13-*cis* retinoic acid, a metabolite of vitamin A, and retinoids in general, can cause significant damage to meibomian glands such as keratinization, glandular atrophy and abnormal secretions if applied topically to or near the eye [103]. Whether conversion of dietary vitamin A to 13-*cis* retinoic acid can also have these adverse effects has yet to be studied.

Clinical trials have reported that topical administration of vitamin B₁₂ to the eye improves dryness symptoms [282, 283]. In a hypothesis-free study looking at medication use and associated risk of dry eye symptoms, those people taking vitamin B₁₂ and folic acid were significantly more likely to have symptomatic dry eye disease [284].

In an uncontrolled study, 50 individuals with diabetes were administered a combination of vitamins C (1,000 mg/day) and E (400 IU/day) for a period of 10 days. An improvement in tear production, stability, density of goblet cell density and squamous metaplasia grade was reported relative to baseline [285]. These effects were attributed to a significant reduction in the levels of nitric oxide measured in lacrimal lavage fluid, which may indicate that these vitamins contribute to a decrease in ocular surface oxidative stress [285]. A randomized controlled trial assessing the efficacy of 8 weeks supplementation of the antioxidants astaxanthin, vitamins A, C, E and herbal extracts in the treatment of patients with dry eye

disease, with follow-up every 4 weeks for 16 weeks [122], found improved Schirmer score (at week 8) and TBUT (at weeks 4 and 16), relative to the control group [122].

Studies have observed an improvement in dry eye discomfort symptoms and signs such as Schirmer score, TBUT and corneal staining after vitamin D supplementation in patients with dry eye disease and low serum vitamin D, especially with those who had disease refractory to conventional treatment [286, 287]. Oral vitamin D supplementation appears to improve the efficacy of topical treatment with vitamin D in patients with dry eye disease resistant to topical lubricants [288].

The previous sections reviewed the impact of specific nutritional components and supplements on the ocular surface. Severe malnutrition, rather than deficiency in a single nutrient, may lead to a significant decrease in tear immunoglobulin A and secretory concentrations, a diminished number of immunoglobulin A-containing cells in lacrimal tissue and a blunted secretory immunoglobulin A antibody response to infectious challenge [289-292]. Sections 3.5 to 3.9 inclusive, therefore, take a more holistic approach to nutrition, reviewing the impact of eating disorders, food intolerance and allergy, as well as various diets on nutrition, and their subsequent impact on the ocular surface. The relationship between the gut microbiome and the ocular surface is also explored.

3.5 Eating disorders

Psychological eating disorders, anorexia nervosa and bulimia nervosa, can result in such severe disease states that patients become deficient in many vitamins and minerals [293]. Anorexia nervosa is defined as a restriction of energy intake and low body weight that is associated with an intense fear of gaining weight and an undue influence of body weight or shape on self-evaluation [294]. Bulimia nervosa is also associated with fear of weight gain and over-emphasis of body weight on self-evaluation. Instead of the restriction of energy intake, however, bulimia nervosa is associated with recurrent episodes, at least weekly, of binge eating

followed by compensatory behaviors to prevent weight gain (e.g., self-induced vomiting, misuse of laxatives and excessive exercise) [294]. The literature is lacking in regard to ocular surface manifestations of bulimia nervosa; therefore, the emphasis in this section is on what is known in the context of anorexia nervosa.

To date, there have been only a few reports that have described ocular manifestations of malnutrition associated with anorexia nervosa; none is a rigorous, comparative, cohort study with adequate sample size. In 1980, a cross-sectional study of 13 patients with anorexia nervosa and 13 controls found no intergroup differences in visual acuity, refractive status and the anterior segment [295]. The authors concluded that lenticular and conjunctival changes were uncommon in patients with anorexia nervosa; however, the small sample size used in this study would render the detection of any mild differences unlikely. A report described ptosis, enophthalmos and lagophthalmos in a case series of five patients hospitalized for multi-organ dysfunction due to severe anorexia nervosa [296]. The authors proposed that severe anorexia nervosa may lead to orbital fat wasting, predisposing to enophthalmos and an inability to attain complete lid closure [296]. Eyelid petechiae have also been reported in one patient with a purging subtype of anorexia nervosa [297]. In a recent large population-based cohort study of almost 80,000 persons in the Netherlands, eating disorders (present in 1.4% of the population) were significantly associated with a 1.64 times higher risk of dry eye disease [111]. Future work should aim to identify, comprehensively, how anorexia nervosa-induced malnutrition manifests in the eye, at what severity of disease each sign is likely to present, the visual and ocular prognosis associated with each sign, and how best to manage ocular complications of anorexia nervosa in the presence of a challenging condition.

3.6 Food intolerance

Food intolerance is a non-allergic, non-immune-mediated reaction and includes metabolic, pharmacologic, toxic and undefined mechanisms [11]. This can include intolerances to lactose,

fructose, fructans, fermentable oligosaccharides, disaccharides, monosaccharides, polyols [298], gluten, food colorings, preservatives and sulfites. Food intolerance has been associated with asthma, chronic fatigue syndrome and irritable bowel syndrome [298]. Unlike food allergy which may manifest within two hours, symptoms relating to food intolerance may take 12-24 hours to manifest [299]. The symptoms can include unexplained bloating, belching, distension, gas, abdominal pain and diarrhea [298]. Intolerance to food additives has been found to result in non-allergic rhinitis in 5% of cases [300]. To date, there are no data on the effect of food additives on the ocular surface, although in a population-based cohort study, lactose intolerance was associated with a trend towards increased dry eye disease (1.8 times greater risk, $p = 0.07$) [111].

3.7 Food allergy

Food allergies involve responses to food proteins such as eggs, milk, peanuts, tree nuts, soy, wheat, crustacean shellfish, and fish [11]. Immunoglobulin E-mediated reactions are reported to affect 5% of children under the age of five years, and 4% of teens and adults [301]; they can range from mild to severe, with severe cases on rare occasion resulting in anaphylaxis and even death. Non-immunoglobulin E-mediated gastrointestinal food allergic disorders are characterized by subacute and/or chronic symptoms, including food protein-induced allergic proctocolitis, enterocolitis syndrome, enteropathy, celiac disease and cow milk-induced iron deficiency anemia [302].

Food allergy might manifest at the ocular surface in the form of allergic conjunctivitis in approximately 14% of people who have food allergies (data from abstract only) [303]. A population-based cohort study reported that food allergy was associated with a 1.4 times increased risk of dry eye disease [111]. The ocular mucosa provides an accessible site for antigen deposition by virtue of its large and exposed surface area [304]. Within seconds to minutes following exposure in sensitized individuals, pro-inflammatory cytokines are released

to stimulate immunoglobulin E. Immunoglobulin E then becomes membrane bound to mast cells, triggering mast cell degranulation and release of histamine, tryptase, leukotrienes and prostaglandins [305]. Clinically, in the early phase, this typically manifests as itching of the ocular surface and eyelids, as well as photophobia, watery discharge, conjunctival redness, chemosis and a tarsal papillary reaction [306]. The late phase involves epithelial infiltrates due to the increased presence of neutrophils, lymphocytes, basophils and eosinophils, and drainage of tears carrying allergens into the nasal passage [306].

Fast foods are typically calorically dense, high in refined carbohydrates, sodium, sugar, cholesterol, and additives, with high concentrations of saturated fat. In a meta-analysis involving pooled data from four studies, consumption of fast food, particularly hamburgers, was found to be associated with rhino-conjunctivitis [307]. While a dose-response could be established for asthma, it could not be established for rhino-conjunctivitis with the limited data available [307]. The association between poor diet and BMI, as well as poorer nutrition are likely to contribute to the manifestation of allergic disease [307], for example, by contributing to chronic inflammatory disease.

3.8 Different diets and the ocular surface

3.8.1 Global influences

Diet can vary markedly depending on the region and the culture. In a quest to identify the secrets to longevity, five places around the world have been labelled as “blue zones”, where life expectancy often exceeds the age of 100 [308]: Loma Linda, CA, USA; Nicoya, Costa Rica; Sardinia, Italy; Ikaria, Greece; Okinawa, Japan. Nine evidence-based common denominators have been identified between these regions, including nutrition [308]. Whether these regions and their associated diets also impact on ocular surface health is unclear. The

subsequent sections review current knowledge regarding global influences on diet and the impact on ocular surface health.

3.8.1.1 Western diet

The Western diet is a modern dietary pattern that is generally characterized by high intakes of red meat, processed meat, pre-packaged foods, butter, salt, candy/lollies, sweets, fried foods, high-fat dairy products, conventionally- or pasture-raised animal products, eggs, saturated fats, refined grains, potatoes, corn, high-sugar drinks, alcohol, but low intakes of fibers, fruits, vegetables, whole grains, fish and seeds [309]. It is also characterized by high-calorie daily intake, sedentary lifestyle, and increased consumption of fast-food. In summary, the Western diet is a relatively high-fat and a high-sugar diet [310]. Based on epidemiological studies, the Western diet is positively correlated with an elevated incidence of obesity, death from heart disease and cancer [311-313] and systemic low-grade inflammation attributed to endotoxemia [314].

In a mouse model, a high-fat diet causes a reduction in peroxisome proliferator-activated receptor γ expression and mitogen-activated protein kinase and nuclear factor kappa-light-chain-enhancer of activated B cells signaling pathway activation. This was associated with an increase in incidence in MGD [315]. In addition, a high-fat diet was linked to pathophysiological changes and functional decompensation of the lacrimal gland in mice [316].

The effect of a high-fat diet on mouse corneal nerve density and resident immune cells has been studied [317]. The summed length of the nerves within the basal nerve plexus was lower in the central and peripheral cornea, the epithelial immune cell density was two-fold higher in the central cornea and the percentage of nerve-associated major histocompatibility complex-II(+) cells in the epithelium was also higher in high-fat diet mice compared to controls. The study concluded that systemic metabolic disturbance induced by a high-fat diet disrupts the neuroimmune status of the cornea [317].

Also in the mouse model, a high-fat diet induced decreased tear production, ocular surface staining and goblet cell loss [318]. It further resulted in corneal epithelial barrier dysfunction and significant squamous metaplasia of the corneal and conjunctival epithelia [318]. The high-fat diet also upregulated key factors that regulate oxidative stress in the ocular surface, and upregulated cell apoptosis in ocular surface epithelial cells [318].

Gut microbial dysbiosis has also been related with a high-fat diet [319]. This diet, perhaps influenced by the gut dysbiosis, has been reported to alter corneal immune cell distribution, corneal response to injury, and genes related to epithelial function and corneal immunity in mice [319].

Further studies are needed to examine the impact of the Western diet on the ocular surface.

3.8.1.2 Mediterranean diet

The Mediterranean diet is inspired by the eating habits of individuals originating from the lands surrounding the Mediterranean Sea. When initially defined in the 1960s, it drew on the eating habits of the populations in Greece, Italy, and Spain. It has also incorporated elements of other Mediterranean diets such as those of North Africa and the Middle East [320]. The principal aspects of the Mediterranean diet include proportionally high consumption of olive oil, legumes, unrefined cereals, fruit and vegetables, moderate to high consumption of fish, moderate consumption of dairy products (mostly as cheese and yogurt), moderate wine consumption, and low consumption of red and processed meat and sugar [321]. The Mediterranean diet has been associated with a reduction in all-cause mortality [322, 323]. It is low in saturated fat with high amounts of monounsaturated fat and fiber. One possible factor for the health benefits of the Mediterranean diet, is olive oil. Olive oil contains monounsaturated fats, most notably oleic acid, which may have a role in protecting blood lipids from oxidation [324]. The Mediterranean diet may help obese people lower the quantity and improve the nutritional quality of food intake, with an overall effect of possibly losing body

weight [325]. Intermittent fasting or food restriction is also present in the three main religions of the Mediterranean Sea [including Catholic Friday, Black Fast and Lent; Muslim Ramadan; Judaism BaHaB (a Hebrew acronym for Monday, Thursday, Monday)].

The Mediterranean diet has been reported to be useful in chronic inflammatory diseases due to its antioxidant and anti-inflammatory properties [326]. It thus might be expected to have benefits in treating inflammatory diseases of the ocular surface, such as dry eye disease.

Stricter adherence to a Mediterranean diet has been associated with a lower likelihood of developing primary Sjögren syndrome [327]. In a separate study, 34 participants with ocular surface discomfort were randomized into one of two interventional arms: (1) a standard intervention group on a Mediterranean diet supplemented with extra virgin olive oil and nuts; (2) an intensive intervention group, based on a hypocaloric Mediterranean diet and an intensive lifestyle program with physical activity and weight-loss. In both groups, OSDI (the Dry Eye Scoring System), TBUT, Schirmer score (after application of topical anesthesia), and the Oxford staining grade improved after six months. However, the intensive intervention group showed greater improvements after six months in TBUT, Schirmer and Oxford staining scores [328]. In contrast, a cross-sectional study of 247 men found that adherence to a Mediterranean diet was associated with more severe dry eye disease [329]. There are several potential explanations for these findings including: the Mediterranean diet differed between the studies; the diet may not be an ideal dietary pattern for control of dry eye, with the effect of alcohol possibly counteracting any possible effect from other nutrients; patients with dry eye disease in the control group may have improved their diet to help alleviate their condition; or these results were confounded by unmeasured variables or a small sample size.

3.8.1.3 African diets

The Central African diet includes plantains, cassava, rice, and yam. The main ingredients of the East African diet are corn, lentils, wheat and vegetables. Meat products are generally

absent. The North African diet includes wheat, olives, vegetables, spices, and sheep meat. Grain, meat, milk, beer, and vegetables are typical products within the South African diet. The West African diet consists of rice, millet, sorghum, brown beans, fruits, and root vegetables such as yams and cassava and is reported to be within the healthiest diets in the world [330]. No studies have to-date reported on the African diet in relation to potential associations with the ocular surface, other than to note that vitamin A deficiency is common in certain African rural areas [331-333].

3.8.1.4 Asian diet

Asia encompasses an expansive continent, with the cuisine and nutrition patterns varying vastly from region to region. In general, Asian Diets, especially traditional Asian Diets, are known to reduce the risk of chronic diseases such as diabetes [334]. There is no clinical evidence in humans about the therapeutic or prophylactic effects of Asian Diet on ocular surface disease, specifically.

3.8.2 Food restriction diets

3.8.2.1 Intermittent fasting

Intermittent fasting involves switching between fasting and eating on a regular schedule and may be undertaken for religious or other reasons. In a study of 25 individuals one month before and one month during Ramadan fasting, tear lysozyme, lactoferrin and alpha amylase were found to decrease significantly with fasting [335]. In another study of 29 males before and after Ramadan fasting, tear osmolarity, OSDI and corneal staining scores increased significantly, while Schirmer scores assessed without topical anaesthesia decreased during the fasting period, compared to non-fasting [336]. A study of 94 healthy adults found no difference in ocular surface parameters, including TBUT [337] with or without fasting, a finding supported by a study of 32 healthy males who were examined at the beginning and end of their

fasting period [338]. Conversely, a study of 40 healthy individuals tested before and toward the end of Ramadan showed a significant decrease in TBUT, as well as an increase in the number of individuals with a positive matrix metalloproteinase-9 test [339].

3.8.2.2 Vegetarianism and veganism

Vegetarianism is the practice of eating no meat and/or fish, and veganism is the practice of not eating or using any animal products or products produced as a result of using animals (such as honey). There is no high level evidence of therapeutic effects on ocular surface health as a result of vegetarianism or veganism, although there are examples of individual case reports describing reversible corneal epitheliopathy in a 27-year-old woman on a vegan diet [340], a 56-year old female vegetarian with herpetic kerato-uveitis and a superimposed pseudomonas infection [341], and of a 6-year-old boy who was a vegan and presented with keratomalacia secondary to vitamin A deficiency [342]. However, these case reports are low level evidence, and further studies are required.

3.8.2.3 Kosher and Halal diets

Kosher diets adhere to Jewish dietary regulations which require that meat must come from ruminant animals with cloven — or split — hooves, such as cows/ox, sheep, goats, oxen, and deer. The Kosher diet also forbids the eating of certain winged animals, permits only those fish which have both fins and scales to be eaten, and forbids consumption of seafood such as shellfish. Halal food is required to be free from any component that Muslims are prohibited from consuming according to Islamic law; as well as food that is processed, made, produced, manufactured or stored using utensils that have been cleansed according to Islamic Law. There are no published reports that examine the impact of these diets on the ocular surface, specifically.

3.8.2.4 Human milk

Breast milk has been used to treat various eye conditions including neonatal conjunctivitis, epiphora, dry eye disease and corneal ulcers [343-349], however, this usually refers to topical application. Breast milk is thought to kill bacterial pathogens found on the ocular surface, including those that are most often responsible for neonatal conjunctivitis, such as *N. gonorrhoea* [345]. In a randomized controlled trial, colostrum was found to reduce the incidence of neonatal conjunctivitis compared to controls without any intervention, but not to the same extent as those given the antibiotic erythromycin [346]. Another investigator masked randomized clinical trial examined the efficacy of topically administered breast milk compared to sodium azulene sulphonate hydrate 0.02% and equivalent clinical efficacy for infants with eye discharge [350]. However, the study has been criticized for including infants with multiple causes of eye discharge including nasolacrimal duct occlusion, viral infections and other transient bacterial infections [351]. Breast milk may also contain cytotoxic proteinases that combat *Acanthamoeba* [352], a vision-threatening keratitis that affects contact lens wearers.

Colostrum has been shown to be effective in the treatment of dry eye disease in animal studies, comparable with the use of cyclosporine [353, 354]. Another study compared breast milk to autologous serum tears and artificial tears on induced epithelial defects on mice and found that breast milk-treated mice displayed the fastest healing [355]. A small case series from Nigeria also reported significant adverse events from the application of breast milk on traumatic eye injuries, but many were treated with other home remedies [356]. Better designed randomized trials would be helpful in delineating the true efficacy of topically administered breast milk in combating ocular surface diseases.

There is also some evidence that breast fed infants have lower incidence of rhinoconjunctivitis and other atopic diseases (eczema, asthma, urticaria) compared to formula-fed infants, but it was unclear how many individuals had eye-specific disease [357].

3.8.2.5 Other diets

The Paleolithic (Paleo) diet tries to mimic the food intake of hunter-gatherers [358]. It focuses on a high-fiber, high-protein diet and limits processed foods. To date, there have been no published reports on the impact of the Paleo diet on the ocular surface. Ketogenic diets also apply a food restriction approach, with a focus on high-fat and low-carbohydrate intake. No published literature exists on the effects of these diets, specifically on the ocular surface. Anti-inflammatory diets are rich in fruits and vegetables and may include foods containing omega-3 fatty acids and other vitamins that may impact ocular surface diseases. Although no published reports exist on anti-inflammatory diets in particular, the effects of omega-3 fatty acids are covered in sections 3.1.1.1 and 3.4.6.

A systematic review and meta-analysis on intentional food restriction and its impact on the ocular surface is reported in section 6.

3.9 The gut microbiome and the ocular surface

Section 3.9 introduces the gut microbiome, with the goal being to understand how it can affect the ocular surface.

3.9.1 The gut microbiome: eubiosis *versus* dysbiosis

The human microbiota refer to the set of organisms that inhabit humans, forming a unique ‘holobiont’ for every individual [359]. The microbiota is influenced by environment, diet, genes, disease and other factors. In turn, signaling molecules from the gut microbiota influence gut motility, energy extraction, epithelial integrity and mucosal immunity [360]. In addition to local effects, the gut microbiota exert distal effects on various organs including the brain and skin [361], and the ocular surface [362].

The gut microbiome is composed of two main phyla, Firmicutes and Bacteroidetes, which account for 90% of the gut microbiome. The Firmicutes-to-Bacteroidetes ratio is often used as

a rough marker of gut dysbiosis. The remaining phyla are Proteobacteria, Actinobacteria, Fusobacteria and Verrucomicrobia [363, 364].

When in an ecologically healthy balance, this complex holobiont ecosystem is termed ‘eubiotic’ (*eu* – Ancient Greek “true” or “good” and *bios* – Ancient Greek “life”) [365]. Ecological shifts within the microbiota can induce imbalance or ‘dysbiosis’ in the gut microbiota which is associated with disease, including chronic disease (Table 3) [366]. Dysbiosis can be induced by many external stimuli including antibiotics, artificial sweeteners, vitamin deficiency, cigarette smoke, saturated (versus polyunsaturated) fats and other anthropogens [366-368] all of which are reviewed in detail elsewhere in this report.

Table 3: The relationship between the gut microbiome and systemic inflammatory diseases

Conditions	Relationship with the gut microbiome (GM)
Primary Sjögren syndrome (SS)	Clinical evidence (reviewed in [364, 369]) - GM changes is modified in SS patients, compared to controls and inverse correlation with ocular and systemic disease severity - There appears as a continuum in GM changes from healthy patients to SS-patients with non-SS DED patients as intermediates
	Experimental evidence (reviewed in [364, 369, 370]) - Dysbiosis in mice induces worsens DED secondary to desiccating stress, compared to non-treated mice - In a mouse model of spontaneous SS, sicca syndrome is worse when the diversity of the GM is low, and maximum in germ-free conditions. In the latter case, passive transfer of immunes cells to mice with no native T or B cells is sufficient to transfer SS-like signs - Probiotics can reduce DED in an animal model - Several peptides from commensal bacteria activate T cells that are sensitive to Ro60 /SSA - Experimental injections of the Escherichia coli outer membrane induce SS-like autoantibodies
Systemic Lupus Erythematosus (SLE)	Clinical evidence (reviewed in [364, 369]) - GM changes in SLE patients compared to matched controls
	Experimental evidence
Rheumatoid arthritis (RA)	Clinical evidence (reviewed in [364, 370]) - GM is less diverse in RA patients than in matched controls (including modified abundance of Prevotella) - Higher frequency of RA patients (32%) with IgG or IgA antibodies reactive with Prevotella
	Experimental evidence (reviewed in [364, 370, 371]) - Modified abundance of Prevotella, Bacteroides, Lactobacillus, and Faecalibacterium reported in RA animal models - Some gut bacteria may modulate autoimmune arthritis by the mean of TH17 cells [372](reviewed in [371])

B27-related disorders, including spondylarthropathy (SpA)	Clinical evidence (reviewed in [373]) - Bowel inflammation in up to 50% of SpA patients, which furthermore increases when arthritis flares up - Dysbiosis in SpA patients compared to matched controls
	Experimental evidence (reviewed in [370, 374]) - GM changes in HLA-B27 transgenic rats compared to wild-type rats, with higher gut permeability - Klebsellia, Enterobacter, Shigella or Yersinia may interact with HLA-B27 lymphocytes, and overgrowth is associated with worsened signs - Similarities between some amino-acids sequences encoded by these bacteria and the HLA B27 molecule - HLA B27 may interact with the metabolism of gut bacteria
Inflammatory Bowel Diseases (IBD)	Clinical evidence (reviewed in [375]) - Dysbiosis in IBD patients compared to matched controls
	Experimental evidence (reviewed in [376] [377]) - Culture of human DCs with stool extract from IBD patients induces Th2 response, correlated with the severity of IBD in the donor - Microbial translocation (and passage LPS and bacterial DNA in the serum) is central if pathogenesis of IBD in mouse models
Graft Versus Host Disease (GVHD)	Clinical evidence (reviewed in [377]) - GVHD is less frequent in patients with mutations in TLR4 loci (sensor of LPS) - Gut decontamination of gram-negative bacteria just before graft reduces the risk of GVHD in humans - Infusion of a polyclonal antiserum against Escherichia coli before graft reduces the risk of GVHD in humans
	Experimental evidence - Gut decontamination of gram-negative bacteria just before graft reduces the risk of GVHD in experimental models
Atopic diseases	Clinical evidence (reviewed in [376]) - Episodes of gut dysbiosis during the first months of life are associated with increased risk of asthma later in life
	Experimental evidence (reviewed in [376]) - Dysbiosis in neonatal mice induces susceptibility to allergic signs in lung - Short chain fatty acid supplementation in dysbiotic mice exhibit reduces the allergic response (in blood and in the lungs) - Probiotics reduce virus-induced and asthma lung inflammations in various animal models - Culture of immune cells with fecal soluble products from 1-month infants at risk for dysbiotic GM favors Th2 cell expansion and reduce Tregs populations

3.9.2 The impact of diet on the gut microbiome

The typical Western diet of low fiber, high energy and which is considered to be at least partly nutritionally deficient, has been associated with a variety of interconnected, chronic non-communicable diseases. Conversely, there is evidence that plant-based diets, including the Mediterranean diet, can improve gut health and modulate non-communicable diseases [378, 379].

Traditional versus Western diets and associated health outcomes were explored in a study comparing the traditional diet of children in Burkina Faso to that of European children [380]. Children from Burkina Faso are typically breastfed for two years compared to one year for European children; upon weaning, their diet reflects a more typical Neolithic diet, being low in fat and animal protein, and rich in starch, fiber and plant polysaccharides, and predominantly vegetarian; in contrast European children consumed the typical Western diet. Burkina Faso children showed greater overall gut microbiome diversity with significant enrichment in Bacteroidetes and depletion in Firmicutes. This diversity of the microbiome ‘fingerprint’ suggests it is protective against inflammation and non-communicable diseases [380].

3.9.2.1 Alcohol

Alcohol consumption adversely alters diversity of the gut microbiome, with enrichment of *Proteobacteria*, *Lachnospiraceae* and *Blautia* and depletion of *Bacteroidetes*, and *Ruminococcaceae*; these changes were maintained following one month of abstinence from alcohol [381]. Additionally, there are increases to intestinal permeability leading to immune system dysfunction with an associated increased production of inflammatory cytokines [382, 383]. However, there is one report that showed rapid changes to the gut microbiome following abstinence from alcohol, suggesting resilience of the gut microbiome [384].

Few studies report on the effect of drinking alcohol on the gut microbiome and within these are suggestions of positive effects for specific forms of alcohol, namely fermented (wine and beer) as opposed to distilled (gin, vodka, etc. with increased levels of alcohol). Beer contains prebiotics and polyphenols including catechins and phenolic acids, while wine is enriched in polyphenols including flavonoids, lignans and stilbenes [383, 385]. One report indicates increased gut microbiome diversity with moderate red wine consumption [386]. However, contrary to this, another study reported lower levels of the beneficial bacteria *Bifidobacterium*, *Blautia coccooides*, *C. leptum*, and *Lactobacillus* in moderate drinkers compared to teetotalers

[387]. These differences may be due to the types of alcohols ingested, and other confounding dietary and lifestyle factors.

3.9.2.2 Food preparation

Beyond food itself, 'diet' incorporates the processes of food production, preparation, preservation and storage, since the state in which food reaches the table determines much about its overall nutritional value.

Just as the human microbiota form a relationship within the body that is essential for human health, plant roots develop relationships with a hugely diverse soil microbiome that offer important nutrients, protect them from disease and pathogens, and help them to adapt to environmental changes. The rhizosphere microbiome is considered the second genome of the plant [388], analogous to the human gut microbiome [389]. Both microbial communities assist in nutrient uptake, modulate immunity, protect from opportunistic pathogens among other functions [388]. Moreover, plant and human microbiomes are intimately linked since microbes from legumes, fruits and vegetables intercalate with the human gut microbiome such that the plant microbiome influences the human gut microbiome and thereby human health [390].

Alterations to the soil through soil transfer or fertilizer use is equivalent to fecal transplantation in humans or antibiotic use. The use of herbicides, fungicides and pesticides in food production can have catastrophic effects on the soil and plant microbiomes, leading ultimately to shifts in the gut microbiome with consequent ramifications for human health [391].

In the chain of mass production, food must be stabilized for transportation and storage. Additives that retain shape, flavor and freshness can be disruptive to gut integrity, contributing to chronic inflammation [392], and immunogenic reactions for some due to gut dysbiosis [393, 394]. Edible nanoparticles used to coat food for shelf-life preservation and inhibition of organic spoilage have been shown to disrupt the gut microbiome homeostasis [395]. An intriguing

‘Cold Chain Hypothesis’ has drawn parallels between increased cold storage of food and the rise of chronic disease [396, 397]. Early exposure of infants to food that has been cold-stored has been associated with greater risk of developing Crohn’s disease in later life [396]. The hygiene hypothesis links increased hygiene to gut dysbiosis and chronic disease [398]. Automated dishwashing compared to handwashing of dishes is suggested to remove an opportunity for robust education of the gut microbiome in children [399].

3.9.2.3 Other factors that can impair the gut microbiome

Beyond diet, other lifestyle factors can impair the gut microbiome and lead to leaky gut and systemic inflammation with potential impact on ocular surface health. A sedentary life, smoking and alcohol are all reported to unfavorably alter the gut microbiome resulting in a leaky mucosa, intestinal and systemic inflammation and reduced production of short chain fatty acids [400].

3.9.3 The gut microbiome and ocular surface disease

Imbalance of the gut microbiome has been associated with eye diseases such as uveitis, age-related macular degeneration, glaucoma, chalazion and dry eye disease [362, 370, 401, 402]. The effect of the gut microbiome on the ocular surface, however, needs to be better explored [403]. Clinical and experimental clues about the impact of gut microbiome on the different types of ocular surface disorders are still scarce in the literature, for all except dry eye disease (4).

Table 4: The relationship between the gut microbiome and ocular surface diseases

Condition	Relationship with the gut microbiome (GM)
Blepharitis	- Ocular microbiota are strongly related with the onset and evolution of blepharitis [103, 404, 405] - Higher rate of <i>H. pylori</i> carriage in the stomach of patients with blepharitis vs controls [406]
Auto-immune scleritis, episcleritis and keratitis	- Scleritis or episcleritis are well known complications of inflammatory bowel diseases [407]

	- These 3 auto-immune conditions are also complications of RA, SLE and other rheumatologic auto-immune, all of them being impacted by GM dysbiosis (see above)
Infectious conjunctivitis and keratitis	<ul style="list-style-type: none"> - GM modifications (more Proteobacteria and less Firmicutes) in patients suffering of fungal keratitis (FK) versus healthy matched controls [408] - naturally resistant to Pseudomonas aeruginosa keratitis can develop corneal infection when grown in germ free mice [409] - Topical application of LPS (from gram-negative bacteria wall) in mice eyes induces increase inflammatory biomarkers in both cornea and conjunctiva, and this can be worsened by antibiotic-induced gut dysbiosis [410] - No specific literature about GM & Trachoma - No specific literature about GM & Viral keratitis and conjunctivitis - No specific literature about GM & Acanthamoeba keratitis
Allergic conjunctivitis and keratitis	- No specific literature about GM & allergic conjunctivitis
Dry eye disease	<p>Clinical evidence</p> <ul style="list-style-type: none"> - GM diversity is reproducibly different between SS-related DED and control participants, but also with non-SS DED patients (reviewed in [364, 411]) - Correlation between Clostridium levels in the GM and positivity to auto-antibodies against La/SSB in the serum of SS patients [412] - Correlation between Prevotella levels in GM and tear secretion in SS-related DED patients [364] - Compared to primary SS, GM has been found very similar in patients with SLE, a common cause of secondary SS [412] - . Improvements of BUT and/or Schirmer score after oral probiotics and/or components described as having anti-oxydant and anti-inflammatory properties (fish oil, lactoferrin, zinc, vitamin C, lutein, vitamin E, γ-aminobutanoic acid) (reviewed in [369]) <p>Experimental evidence</p> <ul style="list-style-type: none"> - Antibiotic-induces dysbiosis in mice increases susceptibility to desiccating stress [413] - Absence of GM (germ-free conditions) increases OS inflammation in experimental dry conditions, while restoration of GM (fecal transplantation) improves experimental DED [414, 415] - Systemic injection of the outer membrane protein A of E. coli in the Harderian and salivary glands induces inflammation in these secretory glands and autoantibodies SSA/Ro and SSB/La, typical of SS [416] - Topical application of probiotics or short chain fatty acids on the eye can improve experimental DED

Animal studies have investigated the effect of diet on dry eye disease. As noted earlier (section 3.8.1.1), mice fed a high-fat diet had ocular surface damage resembling dry-eye, driven by cell apoptosis and CD4+ T cell mediated ocular surface inflammation [318]. Prior studies have shown that high-fat diets alter gut microbiota composition in mice, suggesting that these changes may be related to gut dysbiosis [417], although other factors may also be involved.

The development of MGD has been associated with dyslipidemia in a diet-induced obesity mouse model [418]. In addition to diet, aging-dependent changes in intestinal microbiome composition may be connected to severity of dry eye signs in C57BL/6 male mice [419]. There is as yet no consensus for which specific gut bacteria in animal studies fully correlate with clinical disease.

Human clinical studies have shown results comparable to animals regarding the influence of gut microbiota on dry eye disease [364, 412, 413, 420]. Although some discrepancies exist among these studies, they have generally found parallel correlations between clinical severity of dry eye parameters and gut microbiota, especially in individuals with Sjögren syndrome [364, 411, 413, 420, 421]. People with dry eye disease without any autoimmune etiology showed gut microbiome compositional changes that lay somewhere in between those seen in Sjögren syndrome and controls [364].

Serotonin serves as an ocular surface neuromediator [422], and is dependent on the homeostasis of the gut microbiome. Almost all serotonin produced in the human body is synthesized in the gut, more precisely by enteroendocrine cells, upon modulation by the short chain fatty acids and secondary bile acids produced by spore-forming Clostridiales, some other bacteria and some fungi (*Candida* sp.) [411]. Given the acknowledged role of corneal nerves in the definition [423] and pathogenesis of dry eye disease [422, 424], neurotrophic keratopathy [425], and corneal aging [426, 427], improving ocular surface innervation by restoring gut microbiome homeostasis could be a therapeutic option to improve signs and symptoms of ocular surface disease; research is required to investigate this potential application.

Fecal microbial transplantation in germ-free CD25 knockout mice (a spontaneous dry eye disease model), normalize epithelial staining and goblet cell density [415]. A similar observation has been made in germ-free C57BL/6J mice, in which goblet cell density is reduced, but restored after fecal microbial transplant [414].

Changes to gut commensals have been linked to increased susceptibility to bacterial and fungal keratitis [408, 409, 428, 429]. Whether gut dysbiosis plays a role in other types of keratitis is still unclear.

Further studies are needed to characterize the mechanisms responsible for other ocular surface disease associations.

3.9.4 Modulation of the gut microbiome to improve ocular surface disease

Researchers have investigated modulating the gut microbiome as a therapeutic strategy to improve ocular inflammatory diseases, including those affecting the ocular surface. In general, there are five main approaches [430]: targeting causative bacteria by using certain antibiotics, increasing consumption of dietary components that support beneficial bacteria by using prebiotics, administering live bacterial strains that can restore immune homeostasis by using probiotics, designing and delivering analogues of beneficial bacteria to emulate their effects (by using postbiotics, or replacing the entire gut microbiome population with that from a healthy donor by using fecal microbial transplant. Pre and postbiotics have been studied in one or more subtypes of ocular surface disease. Postbiotics have recently been tested as oral supplement in an animal model of dry eye disease [431] and a clinical trial on fecal microbial transplantation in patients with Sjögren syndrome adds clues to the rationale of this strategy [432].

3.9.4.1 Prebiotics

Administration of prebiotics in isolation to support the health-promoting bacteria in the gut has been investigated in a single randomized controlled, double-masked trial of hydrogen gas-producing milk compared to a beverage with similar flavor, texture and taste in individuals who frequently used visual display terminals [433]. After three weeks, those consuming the test milk had a greater increase in TBUT compared to those in the placebo group, although the

difference was primarily driven by a reduction in TBUT in the placebo group rather than an increase in the test group [433].

3.9.4.2 Probiotics

A more commonly studied approach is to administer probiotics with or without prebiotic additives to support the health of the gut microbiome. A systematic review and meta-analysis concluded that probiotic treatment leads to significant improvements in ocular symptoms associated with allergies, though the authors acknowledged a high degree of heterogeneity [434]. Two clinical trials, one open-label and the other a randomised, double-masked, controlled-trial in patients with allergic conjunctivitis [435] included a conjunctival allergen challenge and treatment with daily oral consumption of mandarin orange yogurt for two to three weeks demonstrated improved ocular redness, chemosis and itching symptoms. Another double-masked, placebo-controlled, parallel, randomized clinical trial found improvements in quality of life, but no gut microbiome changes or inflammatory marker benefits, in rhinoconjunctivitis patients treated with probiotics for eight weeks [436]. Hydrolyzed casein formula, which consists of probiotic *Lactobacillus rhamnosus* GG, has been reported to reduce the occurrence of allergic manifestations (including rhinoconjunctivitis) in children with cow's milk allergy [357, 437]. Interestingly, there was a significantly lower incidence of conjunctivitis in infants of mothers who received the probiotic administration of *Lactobacillus fermentum* CECT5716 (Lc40) [438], but a systematic review found no significant difference in terms of prevention of rhinoconjunctivitis in childhood supplementation with probiotics [439]. Additionally, antibiotic-induced gut dysbiosis has significant long-term effects on corneal development [440]. These impairments in corneal development were reversed with the use of probiotics and fecal microbial transplantation, which strengthened the perceived association between gut microbiota and corneal development [440].

Probiotic use has also been investigated in small preclinical and clinical studies of dry eye disease. *Enterococcus faecium*, a probiotic [441], combined with other prebiotics and vitamins, maintained tear secretion in a rat model of dry eye disease and improved corneal staining, TBUT and subjective symptoms relative to baseline in dry eye patients [201]. These findings are supported by other pilot studies that reported that a combination of prebiotics and probiotics for 28-30 days (dominated mostly by *Lactobacillus* and/or *Bifidobacterium*) yielded greater tear production and tear stability of dry eye patients relative to a control group treated only with artificial tears [442, 443]. The literature lacks reports of clinical trials involving patients with Sjögrens syndrome; however, positive results following probiotic supplementation have been found in a few studies using mouse models of autoimmune dry eye disease [444-446]. All studies used IRT5 probiotics, which combine five known probiotic species: *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus*. Murine tear production and often corneal staining were improved following IRT5 supplementation [444-446]. One study also reported improvement in the murine lacrimal gland histopathology score [444], but no changes were found in goblet cell density [446]. Recently, a study assessing a combination of pre- and postbiotics administered orally showed a significant improvement in signs, compared to placebo, over a four-month treatment period and one extra-month of follow-up [447].

Literature documenting probiotic use in other ocular surface diseases is scarce, but the studies that have been performed do not show significant effects. A study of Lab4 probiotics (two strains each of *Lactobacillus* and *Bifidobacterium* species) in a mouse model of Graves' disease [448] found that Lab4 led to greater amounts of orbital fat in the test group compared to the control group. Another study of IRT5 probiotics following corneal transplantation in BALB/c mice concluded that IRT5 did not prolong graft survival, suggesting that probiotic use has little effect on alloimmunity [444]. Additional work is needed in randomized, controlled

clinical trials with adequate sample sizes before more definitive conclusions surrounding safety and efficacy can be reached.

3.9.4.3 Vitamins and minerals

Dietary supplementation with vitamins and highly nutritional foods has also been reported to positively impact the gut microbiome and ophthalmic diseases [72, 449]. Whilst vitamin D supplementation increases the overall diversity of gut microbiota [450] and a study has shown that oral vitamin D can improve dry eye disease symptoms after two months of supplementation compared to baseline [287], no studies have examined whether changes to the gut microbiome are correlated with this improvement. To date, supplementation of the diet with vitamin C, selenium, lactoferrin, curcumin and flavonoids have all been shown to improve gut health by altering the gut microbiota [451-455]. It is known that these nutritional supplements can be beneficial in reducing symptoms of dry eye disease [72]. However, a systematic review and meta-analysis on the effects of flavonoid supplementation on ocular disorders found a minimal non-significant treatment effect on dry eye disease [456].

In summary, there is limited understanding of the relevant pathophysiological mechanisms associated with the gut microbiome and the ocular surface. The field of modulating the gut microbiome through nutritional changes as an intervention to treat ocular surface disease is also in its infancy. Though encouraging results have been documented in preclinical animal models, translating these findings into human patients may prove challenging due to the natural inter-individual heterogeneity in diet, environment, genetics, disease severity and other lifestyle factors.

4 SYSTEMIC DISEASE INFLUENCED BY NUTRITION AND ITS IMPACT ON THE OCULAR SURFACE

Many systemic disorders are affected by diet and nutrition. Moreover, systemic disorders may themselves further affect the body's uptake, processing and distribution of nutrients [457, 458]. Metabolic disorders are a broad group of disorders in which the body's processing and distribution of macronutrients is negatively altered. They can be inherited or acquired during life. For some, such as type 2 diabetes and hyperlipidemia, diet is an important etiological factor [458]. Cardiovascular disease and chronic kidney disease can result both directly as a complication of metabolic disease, as well as independently as a factor of diet, with downstream effects on the ocular surface [459]. Gastrointestinal disorders can lead to problems with the uptake of nutrients and similarly, these disorders may be exacerbated by poor diet [457].

Many metabolic and gastrointestinal disorders have been associated with an increased risk of ocular surface disease [111, 460, 461]. Although the exact pathophysiological pathways leading to comorbid ocular surface disease are often unknown for these disorders, several general mechanisms may underlie the association. First, the disorders may lead to deficiencies of micro- and macro-nutrients that are important in maintaining ocular surface health. Second, changes in the gut microbiome associated with these disorders may also lead to alterations at the ocular surface (see section 3.9). Third, medications used to treat these disorders have been negatively associated with ocular surface health, such as, decreased lacrimal gland function has been associated with the use of anticholinergic medications, and increased dryness symptoms, with use of proton pump inhibitors [284, 462]. The role of medications on ocular surface health is further discussed in the TFOS Elective Medications & Procedures Impacts Report [102]. Finally, gastrointestinal and metabolic disorders are associated with an increased risk of depression and anxiety [463-465], which may increase pain sensitivity, particularly to exteroceptive stimuli, leading to an increased experience of symptoms, including those from

the ocular surface [466, 467]. The subsequent sections discuss each of these disorders and their known associations with ocular surface disease.

4.1 Metabolic disorders

4.1.1 Obesity

The World Health Organisation estimated that in 2016 there were 650 million obese adults in the world, about 13% of the population at the time [468]. The National Institute of Health defines obesity as a BMI of ≥ 30 kg/m². Several chronic illnesses including type 2 diabetes and cardiovascular diseases are well known complications of obesity [469]. The International Diabetes Federation estimated that 552 million people will suffer from diabetes by the year 2030 [470]. A highly effective long-term treatment option for reversing obesity-associated type 2 diabetes is bariatric surgery [471]. Reportedly, bariatric surgery results in remission of type 2 diabetes in $\geq 70\%$ of patients and prevents the development of diabetes in obese patients [472-474].

Obesity has been associated with various eye conditions including cataract, age-related maculopathy, diabetic retinopathy, glaucoma and ocular surface diseases, such as floppy eyelid syndrome, blepharoptosis and dry eye disease [475-477]. Some of these effects of obesity and BMI on the ocular surface are discussed in this section. The effect of bariatric surgery on the ocular surface is considered by the TFOS Elective Medications & Procedures Impacts Report [102], in the systematic review component of this paper in section 6, and discussed briefly in section 4.1.1.1.

The characteristic feature of floppy eyelid syndrome is hyper-elasticity of the upper eyelids [478]. Many patients with floppy eyelid syndrome are obese and nearly all have obstructive sleep apnea [479]. In floppy eyelid syndrome, the upper eyelid tends to evert, especially when the patient sleeps on one side and, as a consequence, the palpebral conjunctiva

is exposed to the pillow. In patients suffering from floppy eyelid syndrome and obstructive sleep apnea, ocular signs and symptoms may improve following long-term adherence to positive airway pressure. In refractory cases, a significant improvement can be observed after corrective surgery for eyelid laxity [480-483].

Ptosis, also known as blepharoptosis, is defined as an abnormal, low-lying upper eyelid margin with the eye in primary gaze. Blepharoptosis can affect one or both eyes and can be present at birth (congenital) or appear later in life (acquired) [484, 485]. As shown in several case reports, general obesity is accompanied by blepharoptosis in congenital or genetic syndromes [478, 486, 487]. Patients with acquired aponeurogenic blepharoptosis more often have decreased aqueous tear production [488]. In a representative Korean population, obesity parameters such as BMI, waist circumference and percentage body fat were found to be potential risk factors for age-related blepharoptosis [154].

There is a lack of studies specifically investigating the effect of obesity on the tear film, independent of type 2 diabetes [489]. A large population-based cohort study found a higher BMI to be highly significantly associated with less dry eye disease, also after correction for multiple comorbidities and demographic factors [111]. MGD-related tear film instability has been reported in those with polycystic ovarian syndrome and high BMI [490].

4.1.1.1 Bariatric Surgery

Bariatric surgery is often performed in obese patients to achieve sustained weight loss [491]. There has been a growing popularity in such procedures, which has stimulated increased interest in their effects on the eye.

Bariatric surgeries can be categorized as restrictive, malabsorptive, or mixed [492]. Restrictive procedures reduce the functional and/or anatomical size of the stomach with the use of a constricting gastric band or by removing a longitudinal segment of the stomach itself [493]. These procedures, known as the adjustable gastric band (commonly termed 'lap band' when

performed laparoscopically) or gastric sleeve, reduce the capacity of the stomach, predispose to a non-balanced diet, and diminish absorption of certain vitamins and minerals [493]. Malabsorptive procedures bypass a portion of the stomach and/or intestines to iatrogenically limit absorption, again predisposing to deficiencies in many vitamins and minerals [493]. Two common procedures that employ both malabsorptive and restrictive mechanisms are Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch. These procedures that induce malabsorption are more often associated with ocular complications than those of the restrictive variety [493, 494].

Ocular complications following bariatric surgery primarily relate to deficiencies in specific nutrients: vitamin A, vitamin E, vitamin B₁, and copper [495]. Deficiency in vitamin A is the predominant source of ocular surface complications, including conjunctival xerosis with Bitot's spots, corneal xerosis, corneal ulceration, and keratomalacia [493, 496]. It can also induce nyctalopia, which may be the first clinical presentation of vitamin A deficiency [493].

The epidemiology of vitamin A deficiency in patients after bariatric surgery is not well established. The results of several small studies are inconsistent, and the deficiency depends on the type of bariatric surgery [497]. For mixed restrictive and malabsorptive procedures, a prevalence of vitamin A deficiency in 35% of patients 6 weeks after Roux-en-Y gastric bypass versus 18% of patients 1 year after surgery has been reported [498]. In another study of patients who had undergone Roux-en-Y gastric bypass [499], patients reported ocular dryness and night vision changes at rates higher than what were detected for clinically significant vitamin A deficiency. These findings suggest that symptoms typically associated with vitamin A deficiency may onset prior to clinically measurable vitamin A deficiency, which warrants further investigation into their origin and the threshold values used for diagnosis of vitamin A deficiency.

For biliopancreatic diversion, another mixed restrictive and malabsorptive bariatric surgery, the prevalence of vitamin A deficiency seems to be higher. The prevalence of vitamin A deficiency has been reported at 52% for patients 1 year after surgery and 69% for patients 4 years after surgery [500]. There is a progressive increase in the incidence and severity of hypovitaminemia A, D, and K with time after biliopancreatic diversion and duodenal switch [500]. Many of these patients reported compliance with vitamin supplements, emphasizing a possible need for parenteral supplementation of vitamin A in certain cases. In healthy persons who consume an adequate diet, vitamin A reserves are sufficient to meet the body's demands for at least 6 months [493], which may explain why ocular surface complications may appear months to years after surgery if no or poor supplementation occurs.

Regarding restrictive bariatric surgeries, one study found no statistically significant difference in the prevalence of vitamin A deficiency between the adjustable gastric banding group and the control group, which might indicate that there is no increase in the risk of vitamin A deficiency and ocular surface disease after restrictive bariatric surgeries [497].

Two cases of sterile corneal perforation secondary to vitamin A deficiency have been reported after biliopancreatic diversion with duodenal switch, suggesting a need to examine the ocular surface of patients who have undergone bariatric surgery in order to promptly recognize the signs of vitamin A deficiency and avoid serious sight-threatening complications [108]. Corneal melt after refractive surgery in a patient who underwent prior bariatric surgery has been reported [501]. A study of 29 participants with obesity observed for one year following Roux-en-Y gastric bypass surgery found no difference in tear meniscus height, non-invasive TBUT, or meibomian gland morphology [502].

An evaluation of twenty obese patients prior to and 12 months after bariatric surgery, and 22 age-matched healthy controls at baseline only [503], found that obesity was associated with decreased corneal nerve branch density and corneal nerve fiber length. However, these

parameters improved by 12 months after surgery. Further work is needed to understand the mechanisms that underlie changes in corneal nerves in obese individuals and how bariatric surgery results in improved corneal nerve regeneration. Two additional studies have reported no correlation between bariatric surgery and clinical signs of ocular surface disease [504, 505]. As popularity of these surgeries continues to grow, there is an increasing demand for scientists and clinicians to better understand the ocular risks and benefits of bariatric surgery.

4.1.2 Dyslipidemia and hypertension

The association between nutrition and systemic diseases such as hypertension, hyperglycemia and hypercholesterolemia are well known. A population-based cohort study of 79,866 individuals in the Netherlands found that measured hypertension and increasing blood pressure, but not cholesterol levels or hypercholesterolemia, were associated with less dry eye disease (corrected for age, sex, BMI and 48 co-morbidities) [111]. An earlier systematic review included four case-control studies that collectively analyzed 342 individuals with MGD, and reported a positive correlation between dyslipidemia and MGD [506]. However, another prior systematic review included five papers that evaluated outcomes in 809 people [418] and concluded that the relationship between plasma lipid status and MGD was unclear [418]. One cross-sectional prevalence survey on 25,444 men from the USA showed a significant correlation between dry eye disease and self-reported hypertension (odds ratio: 1.28; CI, 1.12-1.45) [507], while the Dry Eye Assessment and Management study that included 535 patients with dry eye from 27 centers found that hypertension and hyperglycemia were not associated with increasing dry eye signs [508]. In a systematic review and meta-analysis of xanthelasma palpebrarum that included 15 case control studies that collectively evaluated 854 people, there was a significant correlation with higher serum levels of total cholesterol and the presence of xanthelasma [509].

Dyslipidemia and MGD, xanthelasma palpebrarum and cholesterol are therefore likely correlated. There are still no studies on the effect of managing cholesterol to prevent or treat MGD. Whether or not hypertension or hyperglycemia is associated with dry eye is still controversial and needs further investigation. It is important for future studies that hypertension is measured and not assessed by questionnaires, as self-reported hypertension appears to be an unreliable phenotype [111, 510].

4.1.3 Metabolic syndrome

For a person to be defined as having metabolic syndrome, they need to have central obesity (defined as waist circumference ≥ 94 cm for men and ≥ 80 cm for women [511]) as well as two of four additional factors including [512]: raised triglyceride levels: ≥ 1.7 mmol/L (150 mg/dL); reduced high density lipoprotein-cholesterol: < 1.03 mmol/L (40 mg/dL) in males and < 1.29 mmol/L (50 mg/dL) in females (or specific treatment for these lipid abnormalities); raised blood pressure (systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg) (or treatment of previously diagnosed hypertension); raised fasting plasma glucose [≥ 5.6 mmol/L (100 mg/dL)] (or previously diagnosed type 2 diabetes).

Two features have been identified as potential causative factors for metabolic syndrome: insulin resistance and abnormal fat distribution, or central obesity [512]. Importantly, metabolic syndrome can have important health implications, including cardiovascular disease and type 2 diabetes [512].

When ocular surface disease was evaluated in a group with metabolic syndrome ($n = 64$), tear osmolarity was higher, dryness symptoms by OSDI were higher, and Schirmer scores and TBUT were lower compared to the control group ($n = 55$) [513]. Metabolic syndrome has also been shown to be associated with peripheral neuropathy and reduced corneal nerve parameters in those with both diabetes and metabolic syndrome compared to those with diabetes only [514]. In the same study, the more severe changes in the metabolic syndrome group indicated

that the observed neuropathic changes may be due to reduced sodium channel permeability and sodium-potassium pump function [514].

4.1.4 Pre-diabetes and type 2 diabetes

Type 2 diabetes, previously referred to as non-insulin dependent diabetes mellitus or adult-onset diabetes, accounts for about 90-95% of diabetes cases. Although several genetic factors are involved, these are amplified by lifestyle (obesity, lack of exercise) and environmental factors [515]. The onset of type 2 diabetes is believed to occur, on average, seven years before confirmation of a clinical diagnosis [516]. By this time, the presence of micro and macrovascular complications is not uncommon [517]. Impaired fasting glucose or impaired glucose tolerance is known as pre-diabetes. The risk of developing diabetes in the pre-diabetes population increases from 30% over 4 years to 70% over 30 years [518]. Lifestyle adjustments or daily metformin intervention can delay the onset of diabetes in these individuals [518, 519].

The whole eye is affected in diabetes with sub-clinical as well as severe clinical complications. The most common sight-threatening ocular complication of diabetes is diabetic retinopathy. In a population-based cohort study of 79,866 individuals, the presence of a diagnosis of diabetes was found to have a moderate but significantly increased risk of dry eye disease (odds ratio: 1.3 (CI: 1.1-1.5)) [111]. However, no clear link between dry eye and HbA1c or glucose levels was found within both diabetic patients and non-diabetics. Also, duration of diabetes was not associated with increased risk of dry eye.

Blinking and correct eyelid positioning play an essential role in maintaining corneal hydration. Blink rates in individuals with type 2 diabetes have been reported to be either decreased (attributed to a decrease in corneal sensitivity in the same cohort) [520] or increased (attributed to a reduced tear thinning time in the same cohort) [521]. Differences in study designs and cohorts may account for the conflicting literature, and moreover, blink rates are notoriously difficult to measure in studies. Both findings and their explanations are plausible

and further investigation is needed to determine if confounders such as age, sex and study location may explain this discrepancy and better characterize this association.

While xanthelasma and floppy eyelid syndrome are directly attributed to other systemic conditions, both have a strong association with type 2 diabetes [522, 523]. More serious complications of the eyelids have been reported in diabetes including rare but severe, life-threatening infections of the lids and surrounding tissues, including mucormycosis [524] and necrotizing fasciitis [525].

MGD is more common in individuals with type 2 diabetes [526, 527]. A large population-based study in Spain involving 937 individuals found that diabetes increased the risk of MGD, particularly asymptomatic MGD [528]. Individuals with type 2 diabetes have been reported to have significantly higher meibography scores indicative of gland dropout [529], more partial glands [526, 529] and a resultant higher lid margin abnormality score [529]. Assessment of rete ridges with confocal microscopy has also shown changes in the gland structure with decreased density and enlargement of individual rete ridges [530, 531]. Meibum lipid composition is also different in those with type 2 diabetes with lower expression of triacylglycerols, wax esters and (O-acyl)-omega-hydroxy fatty acids (OAHFA), and higher expression of cholesteryl esters and phospholipids [532].

Demodex folliculorum is more prevalent on the eyelashes of individuals with type 2 diabetes compared to age-matched controls [533, 534], which was attributed to the general peripheral vascular insufficiency and immunocompromise in type 2 diabetes. Given the association with *Demodex*, it would be expected that individuals with type 2 diabetes are more prone to blepharitis, and this is often stated [535]; however, a population-based cohort study that included 3,284 participants aged over 60-years-old found no association between diabetes and blepharitis [536] while another large scale case control study of 10,093 patients with blepharitis and 40,372 matched controls found that while blepharitis was associated with the

development of metabolic syndrome, it was not associated with diabetes [537]. A systematic review that considered the evidence from three studies evaluating the epidemiology of ocular *Demodex* found an increase in ocular demodicosis in the presence of diabetes in all three studies [538].

Given that one of the most common complications in type 2 diabetes is microvascular damage, it is unsurprising that there is much evidence of microvascular abnormalities in the conjunctiva of patients with type 2 diabetes. Blood vessel dilation [539, 540], reduced and uneven distribution [539-541], increased tortuosity of micro-vessels [542], and altered conjunctival micro-vessel flow velocities [539, 543] have all been described in individuals with type 2 diabetes compared to controls. Increased limbal and bulbar hyperaemia have also been reported [544].

There are other changes to the conjunctival surface in type 2 diabetes. Goblet cell loss and increased conjunctival squamous cell metaplasia has been described in type 2 diabetes compared to controls, as well as associations between goblet cell loss and the level of glycemic control and peripheral neuropathy status [545]. Pinguecula has been found to be more common and more severe in type 2 diabetes [546], which was attributed to other factors related to type 2 diabetes, such as accumulation of advanced glycation end products, microvascular damage and dry eye disease.

Numerous studies have demonstrated alterations to the microbiome of the conjunctiva in type 2 diabetes, with a more complex microbiome than is seen in controls, and that may respond differently to antibiotics [547]. Higher rates of *Staphylococcus aureus* have been isolated [548] and an abundance of *Acinetobacter* were seen compared to healthy individuals [549], which is thought to be related to the effect diabetes has on immune function [550].

Further to the many sub-clinical and clinical changes in individuals with type 2 diabetes, combined with immunocompromise, it is believed that conjunctivitis is also more common in individuals with type 2 diabetes [551, 552].

Severity of diabetes is associated with prevalence of dry eye disease [553], although the heterogeneity in diagnostic criteria in various published studies of over two million participants made it difficult to provide a strong association between diabetes and prevalence of dry eye disease [553]. Patients with type 2 diabetes often experience dryness symptoms [111]. In extreme cases though, apparent tolerance to dryness from poor corneal sensitivity, has led to diabetic neurotrophic keratopathy [554]. Tear stability measured as invasive or non-invasive TBUT has been shown to be significantly reduced with poor glycemic control [545]. A systematic review concluded that poor tear function and stability was associated with diabetes [555]. One study reported a decreased presence of the neuropeptides, substance P and calcitonin gene-related peptide, from corneal nerve terminals into tears in response to neurogenic inflammation for type 1, but not type 2, diabetes [556]. Whether these physiological differences translate into clinical signs and symptoms of dry eye disease in diabetes is to be determined. Diabetic peripheral neuropathy is believed to be the primary cause of lacrimal gland disruption leading to reduced basal tear production in diabetes [557].

Herpetic eye disease and fungal keratitis have been reported to have a higher prevalence in patients with diabetes [558, 559]. Whether or not directly related, corneal basement membrane changes, including accumulation of advanced glycation products, in diabetes, minimize its ability to act as a barrier against infection, and can lead to recurrent epithelial defects [560]. The weakened corneal barrier function has been reported to be associated with higher HbA1c levels [561]. Patients with type 2 diabetes have been shown to be at risk of superficial punctate keratitis, recurrent corneal erosions, persistent epithelial defects and possible endothelial damage [545, 562-565].

A meta-analysis of 15 studies involving more than 1,500 eyes reported an increase in corneal hysteresis and corneal resistance factor in patients with diabetes [566], although it should be noted that it pooled data of both type 1 and type 2 diabetes patients [566]. Further analysis with a different instrument reported similar findings [567, 568] hypothesized to be due to increased corneal viscosity due to glycosylation of corneal proteoglycans and glycosaminoglycans, in those with diabetes [569].

Corneal sensitivity threshold has been shown to be reduced in patients with type 1 and 2 diabetes when measured by both contact and non-contact esthesiometry [555, 570-572]. A strong association has been reported between corneal sensitivity, increasing age and poor glycemic control [573]. Unsurprisingly, corneal sensitivity has a well-established correlation with corneal sub-basal nerve plexus in type 2 diabetes [570]. Two large systematic reviews of more than 3,000 patients with diabetes (type 1 and 2 combined) identified corneal nerve fiber changes compared to controls, including reduction in nerve fiber density, nerve fiber length, nerve beading density and inferior whorl length [574, 575]. The subclinical changes in the corneal nerve plexus are associated with the presence of diabetic peripheral neuropathy [576], suggesting a potential role for corneal confocal microscopy in early detection for timely treatment of neuropathy in at-risk patients. The corneal endothelial changes in type 2 diabetes are still a matter of discussion as some studies have reported increased polymegathism and pleomorphism, while others did not observe differences compared to control participants [563, 577, 578].

4.2 Cardiovascular disease

Cardiovascular disease is the cause of death for 17.7 million people worldwide per year [579] and is highly correlated with various aspects of nutrition [580]. Acute myocardial infarction is a late consequence of the disease, while dysfunction of the microcirculation of the body manifests early in the disease [581]. In a population-based cohort study of 79,866 participants, cardiovascular disorders were found to be associated with dry eye disease [111]:

specifically, atherosclerosis (odds ratio: 1.79 (CI: 1.37-2.35), $p < 0.001$), thrombosis (odds ratio: 1.37 (CI: 1.12-1.68), $p = 0.002$), heart arrhythmia (odds ratio: 1.53 (CI: 1.42-1.65), $p < 0.001$), and aorta aneurysm (odds ratio: 1.71 (CI: 1.17-2.49) [111].

Given its accessibility, the conjunctival microcirculation has been studied for parameters such as diameter, axial velocity, blood volume flow and wall shear rate [582, 583]. Alterations of these variables were noted in cardiovascular disease, in diabetic microvasculopathy [584] and unilateral ischemic stroke [585]. In acute myocardial infarction, lower axial velocity and wall shear rate were found compared to controls [586]. These findings are suggestive of endothelial dysfunction, as well as atherosclerotic changes, contributing to reduced axial velocity in the conjunctival vessels [586]. A reduction in wall shear rate can lead to abnormal vascular wall remodeling and is related to plasma viscosity [587].

4.3 Chronic kidney disease

Chronic kidney disease is characterized by a gradual loss of kidney function over a period of greater than three months, accompanied by a decrease in kidney estimated glomerular filtration rate and proteinuria [588]. Chronic kidney disease has been linked to multiple etiologies that are linked to nutrition, including diabetes, hypertension and glomerulonephritis. The severity of the disease can be staged according to the estimated glomerular filtration rate. Stages 3-5 describe the terminal stage of the disease known as chronic renal failure [589], that is treated with hemodialysis. Patients with stages 3-5 will present with anemia, reduced appetite, abnormal calcium and phosphorous metabolism, electrolyte disturbance and acid-based imbalance [589].

Chronic kidney disease affects between 30-50% of people with diabetes [590] and can contribute to neurological complications of both the central and peripheral nervous systems [591]. The presence of both diabetes and chronic kidney disease can exacerbate the subsequent peripheral neuropathy [592]. In the cornea, nerve loss has been found to be significantly greater

in those with type 2 diabetes and chronic kidney disease compared to those with diabetes alone, with the reduction in corneal nerve parameters was associated with the decline in kidney function as well as peripheral neuropathy status [593].

In a study exploring dry eye disease parameters and the tear proteome in 20 patients with non-diabetic stage 3-5 chronic kidney disease undergoing hemodialysis and 10 healthy controls, patients with chronic kidney disease were found to have a higher OSDI score [594]. They were also found to have a lower tear volume with the Schirmer score, a lower TBUT and tear meniscus height, and greater meibomian gland dropout [594]. These findings are supported by other studies [595-597]. The tear analysis indicated that the differentially-expressed proteins were involved in lipid metabolism, inflammation and immune responses [594], suggesting that changes in these pathways due to chronic kidney disease may be reflected in the tear film, contributing to the signs and symptoms of dry eye disease. One study also reported a decrease in tear osmolarity following hemodialysis [598].

Patients with chronic kidney disease undergoing hemodialysis have been reported to have increased central corneal thickness and reduced endothelial density, more so in those with elevated urea levels, compared to those not undergoing hemodialysis and healthy controls [599]. The authors hypothesized that these changes were due to elevated toxins in the blood and therefore the aqueous humor, having a downstream effect on the corneal endothelium [599].

Corneal and conjunctival changes in chronic renal failure may be a result of metastatic calcification and chronic inflammation, and may be a result of the disease that triggered the chronic renal failure, as well as the chronic renal failure itself [600]. Calcium salts are deposited beneath the corneal epithelium as a result of limbal blood flow [600], giving the characteristic band-like keratopathy appearance. An elevated level of calcium phosphate products in the serum has been found in patients with band keratopathy [601]. Treatment involves managing

the underlying disease, as well as removing any deposits in symptomatic patients using superficial keratectomy, with or without ethylenediaminetetraacetic acid as a chelating agent [600]. Calcium-phosphate deposits can also be found in the conjunctiva within the interpalpebral region [601], as well as squamous metaplasia as evaluated with impression cytology [602, 603].

4.4 Gastrointestinal disease

Nutrition and gastrointestinal function are closely related [604]. The chief purpose of the gut is to digest and absorb nutrients. Chronic gastrointestinal disease therefore can commonly result in malnutrition [604]. This chronic malnutrition can further impair digestive and absorptive function [604]. In a population-based cohort study of 79,866 participants, many gastrointestinal diseases were associated with dry eye [111]: stomach ulcers (odds ratio: 1.68 (CI: 1.52–1.86) $p < 0.001$), Crohn's disease (odds ratio: (CI: 1.51–2.70) $p < 0.001$), ulcerative colitis (odds ratio: 1.61 (CI: 1.29–2.01) $p < 0.001$), celiac disease (odds ratio: 1.66 (CI: 1.27–2.19) $p < 0.001$), lactose intolerance (odds ratio: 1.84 (CI: 0.96–3.54) $p = 0.07$) and diverticulosis (odds ratio: 1.71 (CI: 1.20–2.44) $p = 0.003$) [111].

4.4.1 Inflammatory bowel disease

Inflammatory bowel disease is a chronic immune-mediated systemic disorder which comprises Crohn's disease and ulcerative colitis [605]. Crohn's disease can affect any part of the gastrointestinal tract, while ulcerative colitis affects the large intestines [605]. Inflammatory bowel disease can manifest outside of the gastrointestinal tract in 5-50% of patients [606], including the musculoskeletal, cutaneous and ocular systems [605]. Approximately 2-5% of patients with inflammatory bowel disease will present with ocular surface manifestations [605], including episcleritis, scleritis and uveitis [605] due to the formation of antigen-antibody complexes that target the ocular tissues [607]. Ocular manifestations are associated with

musculoskeletal manifestations [608]. Episcleritis is associated with ongoing intestinal flare, although it may arise before or after the intestinal manifestations of the disease [605]. Patients with inflammatory bowel disease have also been reported to have thinner corneas [609] and signs and symptoms of dry eye disease [610].

4.4.2 Celiac disease

Celiac disease is an immunologic non-immunoglobulin E-mediated reaction to certain foods, and as such is both a food intolerance and autoimmune disorder [611]. Its prevalence ranges from 0.15% to 2.67%, which varies depending on the country studied and whether serologic testing or biopsy was used for diagnosis [611]. It has been defined as a permanent intolerance to gluten which is a storage protein from wheat, barley, spelt and rye [611]. Ingestion of gluten in susceptible individuals causes a chronic inflammatory state of the proximal small intestinal mucosa [611], which is where gluten first encounters the mucosal immune system.

The ocular manifestations of celiac disease may be due to the primary disease, or secondarily due to resultant deficiency in vitamins and minerals such as vitamin A, D and calcium [612]. In a cross-sectional descriptive study of a German hospital database analysis, a total of 272,873 patients with eye conditions were evaluated [607]. The prevalence of ocular complications in 72 individuals with celiac disease was explored in one study [607]. The most common diagnosis was dry eye disease (32%), and the profile of ophthalmological manifestations was considered similar to that seen in inflammatory bowel disease [607]. None of the patients with dry eye disease had vitamin A deficiency [607], suggesting that the dry eye may be autoimmune in origin, rather than secondary to dietary restrictions. In a cross-sectional study of 36 adults with celiac disease and 35 age- and sex-matched healthy controls, patients with celiac disease had reduced corneal endothelial cell density [613] as well as changes to other ocular parameters, such as anterior chamber depth. In a study of young children with

celiac disease, a decreased Schirmer score and TBUT was reported, relative to controls [614], suggesting a predisposition to dry eye disease from a young age. Similar dry eye results were found in adult cohorts [615], as well as significant squamous metaplasia of the conjunctival epithelial cells and reduced goblet cell density [94], supporting the existence of ocular surface disease in celiac disease.

While there are case reports on the impact of a gluten free diet on ocular surface complications [616], there are no higher levels of evidence available. As discussed in section 3.1.1.4, reduction of gluten from the diet in affected individuals might reduce ocular surface inflammation due to overall reduced disease severity [94].

4.4.3 Irritable bowel syndrome

Irritable bowel syndrome is a functional bowel disorder, and therefore part of a spectrum of chronic gastrointestinal disorders characterized by abdominal pain, bloating, distention and/or bowel habit abnormalities such as constipation and diarrhea [617]. Diagnosis requires symptoms to have commenced at least six months prior, and to be present for at least the previous three months [617]. A meta-analysis found a prevalence of 11.2% (CI: 9.8%–12.8%) [618], depending on the country and diagnostic criteria used. The prevalence was higher in women (odds ratio: 1.67; CI: 1.53–1.82) and lower for people over the age of 50 years (odds ratio: 0.75; CI: 0.62–0.92) [618]. The pathophysiology of irritable bowel syndrome is poorly understood, although it is thought to be due to inflammation, with increased numbers of inflammatory cells found in the colonic mucosa of patients with the condition [619]. Treatment is based on symptom type and severity and includes lifestyle modifications such as exercise, stress reduction and attention to impaired sleep [617]. In terms of dietary management, dietary fiber is key, and in some cases, dietary restriction of gluten [617]. Dietary restriction might have a role in improving symptoms of irritable bowel syndrome [620].

In a population-based cross-sectional association study of 3,824 women from the Twins UK cohort, aged 20–87 years, irritable bowel syndrome had one of the highest effect sizes for dry eye disease ($p < 0.005$), with a prevalence of 20% and an odds ratio of 2.24 (CI: 1.76-2.85) [461]. This strong association was similarly reported in a population-based cohort study of 79,866 participants [111]. In two cross-sectional studies in the Netherlands of 648 patients with dry eye disease, irritable bowel syndrome was associated with relatively few signs but high symptomatology in dry eye disease [621, 622].

Ocular manifestations have been linked to the underlying inflammatory pathogenesis. In a case-control study of 95 patients with irritable bowel syndrome and 276 healthy controls, the former were more symptomatic for dry eye disease, and more likely to have a reduced TBUT and Schirmer score [623]. These findings have been corroborated by other cohort [624-626] and epidemiological studies [111], although other studies have not found an association [508].

A large twin study found greater within-twin correlation for monozygotic twin pairs than dizygotic twin pairs, as well as greater cross-twin cross-trait correlations, suggesting shared genetic factors between irritable bowel syndrome, dry eye disease and other chronic pain syndromes [627].

4.5 Cancer

Many cancers, such as oesophageal, stomach, colorectal (or bowel) and liver cancer have a close association to nutrition and the gastrointestinal system [628, 629]. Cancer has multiple effects on the body beyond the local tumor site, such as weight loss, decreased resistance to infection, physical compression on neighboring blood vessels and nerves, and metastasis. The ocular surface, having a rich nerve supply, vasculature in the choroid and comprising numerous different cell types, is therefore theoretically vulnerable to all these effects. There is evidence of both metastasis and infection related to the cancers listed above influencing the ocular surface.

While metastasis of cancer to the eye is uncommon, and even more so for gastrointestinal cancers [630], there are numerous reports of metastases impacting the ocular surface. Eyelid tumor metastasis has been reported secondary to esophageal [631] and rectal cancer [632], presenting as large mass on the upper lid, in one case first being misdiagnosed as a chalazion [631]. Iris metastases have been reported secondary to esophageal cancer [633, 634], presenting as a visible iris mass, and in some cases, also hyphema, discomfort, conjunctival hyperemia, and cells in the anterior chamber. Scleral metastasis has been reported secondary to esophageal cancer [635], presenting as ocular swelling, conjunctival hyperemia and excessive tearing. While not part of the ocular surface, orbital metastases reported from colon [636-640], rectal [641, 642], esophageal [643] and liver [644] cancers have presented with ocular surface symptoms including proptosis, ptosis, eyelid edema, conjunctival hyperemia, eye pain, and a fixed pupil, as well as yellow, jaundiced conjunctiva in the case of liver cancer metastasis. A jaundiced conjunctiva has long been recognised as a sign of a variety of liver diseases including cancer [645].

In addition to metastasis, infection is also a risk for individuals with cancer. Rare ocular infections, panophthalmitis (due to *Clostridium Septicum*) and endophthalmitis (due to *Candida albicans*) have been reported in individuals with colon [646] and esophageal [647] cancer respectively, untreated by chemotherapy.

More subtle, sub-clinical effects of gastrointestinal cancers on the ocular surface have also been revealed in studies investigating the eye as a biomarker for systemic conditions. Corneal nerve fiber length, density and branch density were all found to be reduced in individuals with upper gastrointestinal cancer prior to commencement of chemotherapy compared to age-matched controls [648]. This was thought to be a reflection of systemic peripheral neuropathy associated with cancer but there was no corresponding reduction in corneal sensitivity [648].

Individuals with colon cancer have also been reported to have higher rates of the tear protein lacryglobin, a small protein of unknown function [649].

These sub-clinical signs, while of interest to researchers, are not of immediate clinical relevance. Both the metastases and infections described here are of clinical importance, but are rare, reflected by the scant evidence available, all in the form of case reports. Most potential impacts of cancer on the ocular surface are likely to be overshadowed by the side-effects of chemotherapy. However, in some of the cases described here, the ocular surface and adnexa signs were the presenting complaint, leading to the investigation and discovery of the primary gastrointestinal cancer. Therefore, eyecare practitioners should be cognizant of this as a possibility.

5 EPIGENETICS

Epigenetic modifications are reversible yet stable, modifications to DNA that can be inherited through generations and mutually influence, and are influenced by environment, behavior, aging, inflammation, drugs, oxidative stress, seasonal changes, circadian rhythm and nutrition, among other stressors [650].

Nutrition influences epigenetic modifications in a hierarchy of levels: from acting as a source of metabolites and co-enzymes, vitamins and cations, and methyl donors necessary for DNA and histone methylation; to providing bioactive food components leading directly to DNA methylation and histone modification; to affecting systemic metabolism that modifies local cellular environments and hence epigenetic patterning [651]. Homocysteine is critical for regulating key epigenetic mechanisms, and hence impaired homocysteine metabolism can lead to increased free radicals, oxidative stress and systemic inflammation [652]. Methionine and choline in the diet influence homocysteine plasma levels, while vitamin status (folate, vitamins B₂, B₆, B₉, B₁₂) influences the relation between methionine and homocysteinemia [652].

Accumulating evidence indicates that the etiology of ocular surface inflammatory disorders lies, in part, in deleterious epigenetic modification [650]. Drawing together inflammation, immunity, epigenetics, and nutrition can provide a deeper understanding of the development and treatment of ocular surface disorders.

Emerging evidence suggests epigenetic mechanisms are important in the pathophysiology of ocular surface disease [653]. There is evidence suggesting that epigenetic modification plays a key role in the development of pterygium [653-655], but since environmental factors (ultra-violet irradiation) rather than nutrition appear to play the dominant role, this is beyond the scope of this section.

The role of epigenetics in keratitis is not well explored. However, it is known that the innate immune response plays a pivotal role in ocular surface inflammation with toll-like receptors influencing the innate response through decreased histone deacetylation leading to increased production of inflammatory interleukins and tumor necrosis factor that are implicated in development of microbial keratitis [653]. The contribution of nutrition and epigenetic modification to keratitis can be inferred from studies that suggest type 2 diabetes-associated microbial keratitis is driven, in part, by epigenetic modifications (directly or indirectly as a result of nutritionally driven disease) [656].

Other than oral vitamin B₁ and cobalamin (endogenous B₁₂) relieving dry eye symptoms [657] and the fact that cobalamin serves as a cofactor in the conversion of homocysteine to methionine (and hence is implicated epigenetically [657] in regulating DNA methylation [652]), there remains very little evidence at this time of epigenetic involvement in dry eye disease.

6 SYSTEMATIC REVIEW AND META-ANALYSIS: THE EFFECT(S) OF DIFFERENT FORMS OF INTENTIONAL FOOD RESTRICTION ON THE OCULAR SURFACE

6.1 Introduction

Intentional food restriction may occur during religious fasting, in different forms of diets, following surgical procedures and in certain medical conditions [504, 613, 658, 659]. Despite increasing general interest in food-restricted diets [660], their effects on ocular surface health remain unclear. The aim of this systematic review was to investigate the safety and impact of different forms of intentional food restrictions on the ocular surface.

6.2 Methods

This review was prospectively registered on PROSPERO (CRD42022297045) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement [661].

6.2.1 Search method

PubMed and Ovid Embase electronic databases were searched from inception to 9 December 2021. Complete search strategies are provided in Supplement I. In addition, the reference lists of included studies were screened to identify any potential studies that were not captured in the initial searches.

6.2.2 Eligibility criteria

Study designs eligible for inclusion were randomized controlled trials, pseudo-randomized controlled trials, non-randomized intervention studies, cohort studies, cross-sectional studies, case-control studies and pre-post intervention studies. The studies that were included assessed the efficacy and/or safety of any form of intentional food restriction on a parameter (symptom or sign) relevant to ocular surface health, relative to no intentional food restriction, including a

standard (e.g., normal diet) or control (e.g., sham surgery or placebo diet) condition. Only full-text studies published in English were included; conference abstracts and animal studies were ineligible. The types of ‘intentional food restriction’ eligible for inclusion were total caloric restriction, fat-restricted diet, sodium-restricted diet, gluten-free diet, lactose-free diet, protein-restricted diet, vitamin-restricted diet, carbohydrate-restricted diet, Palaeolithic diet, anti-inflammatory diet, religious meat restriction diet (e.g., kosher and halal), intermittent fasting, fad diets, ketogenic diet, vegetarian and vegan diets, food elimination diets, religious fasting, intermittent food restriction, surgical interventions (e.g., bariatric surgery) and medical conditions (e.g., bulimia and anorexia). Diets defined by geographical location-based general eating patterns (e.g., Mediterranean diet, Asian diet) were excluded.

6.2.3 Study selection

Citations retrieved from the electronic databases were collated into an EndNote library. After removal of duplicates, the library was imported into Covidence [662]. Two reviewers (two of SS, BC, MW, LD, and MM) independently performed title/abstract screening; studies judged as ‘eligible’ or ‘potentially eligible’ progressed to full-text screening. Two review authors (two of SS, BC, MW, and LD) independently screened the full texts and decided whether to ‘include’ or ‘exclude’ the studies, based on the pre-defined eligibility criteria. Discrepancies were resolved by discussion (SS and LD).

6.2.4 Data extraction and management

Two reviewers (SS and one of BC, MW or LD) independently extracted the predefined key study data (Supplement I) from eligible studies; discrepancies were resolved by discussion (SS and LD). Extracted data was exported to Cochrane Review Manager (RevMan Version 5.4) software [663].

6.2.5 Risk of bias assessment

To account for the inclusion of different study designs, a variety of risk of bias tools were used for the quality assessments. Two review authors (SS and one of BC, MW or LD) independently performed the assessments; discrepancies were resolved by discussion. The risk of bias tools used were: ROBINS-I tool for non-randomized intervention studies [664], Newcastle Ottawa scale for cohort and case-control studies [665], National Heart, Lung, and Blood Institute (NHLBI) tool for cross-sectional studies and pre-post studies with no control group [666].

6.2.6 Primary and secondary outcomes

The primary outcome was change from baseline in dry eye symptom score, measured using a questionnaire or visual analogue scale. Secondary outcomes were the change from baseline in TBUT (secs), tear osmolarity (mOsm/L), degree of meibomian gland atrophy (%), degree of anterior blepharitis, corneal staining scores, Schirmer score (mm), degree of conjunctival hyperaemia, quality of life, and incidence of ocular adverse events.

All outcomes were considered for the following follow-up periods: (i) short-term: measured the study outcome(s) at 7 to 28 days inclusive of the intentional food restrictions; and (ii) longer-term: measured the study outcome(s) at more than 28 days after intentional food restrictions.

6.2.7 Data synthesis and analysis

Primary and secondary outcome data were extracted as the mean change from baseline and standard deviation (SD) of the change across the intervention and control groups. When change from baseline data were not available, study endpoint data were extracted.

Meta-analyses were performed using Cochrane Review Manager software [663] for each intervention category where data were available, when at least two studies reported data in a consistent format and a pooled analysis was deemed clinically appropriate (e.g., for studies

where the intervention and the clinical population were similar). For pre-post studies, meta-analysis was performed using the generic inverse variation effect estimation method [667].

Clinical and methodological heterogeneity were assessed by evaluating the study design, participant characteristics and intervention type. Statistical heterogeneity was quantified using the I-squared (I^2) statistic, which quantifies the percentage of variability across all studies. An I^2 statistic $>60\%$ and Chi-squared test p value < 0.10 defined significant heterogeneity [668]. If there was only one study or data pooling was not appropriate (i.e., in the presence of significant heterogeneity), a narrative summary of the key findings was provided.

The certainty of the body of evidence for both the primary and secondary outcomes were assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach and judged as high, moderate, low, or very low. The reason(s) for downgrading the certainty estimates are reported in the ‘Summary of findings’ (Table 5).

6.3 Results

6.3.1 Characteristics of included studies

The electronic database searches yielded 7,250 citations (Figure 1). After removing duplicates ($n=1357$), title and abstract screening was performed on 5,893 citations. Of these, 75 citations underwent full-text screening, and 25 studies met the pre-specified eligibility criteria and were included. A list of studies excluded at the full-text review stage and the primary reason for exclusion are provided in Supplement I.

All 25 studies [295, 335-339, 503, 504, 613, 659, 669-683] were full-text articles published between 1951 and 2021; their key characteristics are summarised in Table 6. The studies were conducted in six countries: UK ($n = 3$) [503, 669, 670], Turkey ($n = 3$) [613, 673, 681], USA ($n = 2$) [659, 675], United Arab Emirates ($n = 1$) [339], Brazil ($n = 1$) [504], and Iran ($n = 1$) [337]. Fourteen studies did not report their study location [295, 335, 336, 338, 671, 672, 674,

676-680, 682, 683]. The study designs were pre-post intervention (n = 14) [335-339, 503, 669, 670, 672, 676-678, 681, 683], cross-sectional (n = 8) [295, 613, 659, 671, 673, 674, 679, 680], non-randomized interventional (n = 1) [675], and retrospective (n = 1) [504] or prospective (n = 1) [682] cohort.

The types of exposures evaluated were religious fasting (n = 14) [335-339, 672, 673, 676-679, 681-683], bariatric surgery (n = 4) [503, 504, 669, 670], short-term fasting (12-hours, n = 1) [680], riboflavin depletion diet (n = 1) [675], anorexia nervosa (n = 4) [295, 659, 671, 674] and celiac disease (n = 1) [613].

In total, 1,181 participants were enrolled across the 25 studies with individual study sample sizes ranging from 14 to 134 participants. Twenty-three studies [295, 336-339, 504, 613, 659, 669-678, 680-683] reported sex distribution of the recruited or study completed participants; female (n = 533), male (n = 437). The unit of analysis was a single eye in seven studies [336-338, 676, 679, 681, 683], both eyes in seven studies [504, 613, 672, 673, 677, 678, 682], per participant in two studies [671, 674], and unclear in nine studies [295, 335, 339, 503, 659, 669, 670, 675, 680].

6.3.2 Risk of bias assessment

Supplement I provides detail and justification for the risk of bias assessments. The 14 pre-post intervention studies were judged to have poor (n = 13)[335-339, 503, 670, 672, 676-678, 681, 683] or fair (n = 1) [669] quality due to studies not reporting study eligibility criteria, sample size calculations and/or information related to masking of the outcome assessors. The eight cross-sectional studies [295, 613, 659, 671, 673, 674, 679, 680] were judged to have poor quality due to not defining the study population clearly, absence of reporting sample size calculations and/or insufficient information about whether outcome assessors were masked. The two cohort studies [504, 682] were judged to have unsatisfactory quality due to absence of any information related to the derivation of the study cohort, ascertainment of the exposure,

and adjustment for confounders. The non-randomized experimental study [675] was judged to have a serious risk of bias because of confounding and potential biases in the selection of the reported results.

6.3.3 Effects of interventions

6.3.3.1 Religious fasting

Fourteen studies investigated religious fasting using pre-post [335-339, 672, 676-678, 681, 683], cross-sectional [673, 679], or cohort study designs [682]. All studies assessed Ramadan fasting, which involves abstaining from food, water and smoking from dawn to sunset for a period of 29 or 30 days [336, 683]. Absence of liquid intake during the daytime has been found to cause changes to body fluid and hemodynamics [338]. As a result of this dehydration, it has been hypothesized to alter tear film dynamics and provoke ocular symptoms [336]. The control group for the cross-sectional and cohort studies comprised non-fasting individuals. Combined, these studies included 725 participants; sample sizes ranged from 15 to 134 participants [335-339, 672, 676-678, 681, 683]. Of the 14 included studies, nine [335, 672, 673, 677-679, 681-683] did not measure any of the expected primary or secondary outcomes.

Primary outcome

Two studies measured dry eye symptom scores using the OSDI questionnaire (Figure 2) [336, 339]. Pooling data from these pre-post studies was not deemed appropriate due to high statistical heterogeneity ($I^2 = 78\%$, $p = 0.03$), in the presence of divergent study effects and differences in sex distribution of the included participants. The studies differed in their design, with one study [339] collecting data from one week prior to the beginning of Ramadan fasting and then in the third or fourth week of fasting between 12 and 5pm. The other study design involved collecting data two weeks prior to the beginning of Ramadan fasting and then in the first week of fasting, with all measurements captured between 4 and 5PM[336]. One study [339] reported no significant difference in dryness symptoms between Ramadan fasting and

the non-fasting period (Figure 2), whereas another study [336] reported lower symptom scores during non-fasting compared to Ramadan fasting (29 participants; mean difference mean difference: 5.60 units; CI: 1.84 to 9.36; $p = 0.004$). The GRADE certainty of evidence for this outcome was judged as very low (Table 5).

Secondary outcomes

Four studies evaluated TBUT (Figure 3) using fluorescein [336, 338, 339] and non-invasive (no fluorescein) [337] methods. Pooling data from these four studies [336-339] was deemed inappropriate due to high inter-study heterogeneity ($I^2 = 72\%$, $p = 0.01$). This could be a result of differences in sex distribution across the included studies or variation in outcome measurement techniques (fluorescein versus non-invasive). There were also variations in follow-up periods during Ramadan fasting between the studies; first week of Ramadan [336], third or fourth week of Ramadan [339] and last week of Ramadan [337]. Further, one study [338] collected data over the course of the day, at the beginning (8am and 8:30am) and end of Ramadan fasting (4:30pm and 5pm).

One study [339] reported lower fluorescein TBUTs after 3-4 weeks of Ramadan fasting compared to non-fasting (40 participants; mean difference: -1.70s CI: -2.93 to -0.47; $p = 0.007$). No significant difference in fluorescein TBUT after one week of Ramadan fasting compared to non-fasting was reported in another study (Figure 3) [336]. Another study [337] reported no difference in non-invasive TBUT during last week of Ramadan fasting compared to non-fasting (Figure 3). Further, one study [338] reported no difference in TBUT measured at the beginning (8:00am - 8:30am) and end of Ramadan fasting (4:30pm - 5:00pm) over the course of a day (Figure 3).

Four studies evaluated Schirmer scores (Figure 4) [336, 338, 339, 676], measured using with anaesthesia [338, 339], without anaesthesia [336], or using both techniques [676]. Pooling data from these four studies [336, 338, 339, 676] was not deemed appropriate due to high inter-

study heterogeneity ($I^2 = 64\%$; $p = 0.04$). This could be due to differences in sex distribution across the included studies, differences in outcome measurement techniques (with or without anaesthesia) and variation in follow-up timepoint reported during Ramadan fasting measures across the included studies. One study [336] reported lower Schirmer scores measured without anaesthesia after one week of Ramadan fasting compared to non-fasting (29 participants; mean difference: -4.20; CI: -6.43 to -1.97; $p = 0.0002$). No difference in Schirmer scores measured using both with/without anaesthesia during Ramadan fasting compared to non-fasting was reported in another study, but it was unclear at what timepoint the follow-up occurred [676] (Figure 4). Another study [339] reported no difference in Schirmer scores measured using anaesthesia after 3-4 weeks of Ramadan fasting compared to non-fasting (Figure 4). Likewise, one study [338] reported no significant difference for Schirmer scores measured with anaesthesia at the beginning and end of fasting (Figure 4).

Based on data from one study [336], tear osmolarity was higher during Ramadan fasting compared to a non-fasting period (29 participants; mean difference: 7.70 mOsm/L; CI: 1.58 to 13.82; $p = 0.01$). A separate study [339] reported no difference (40 participants; mean difference: 0.00 units; CI: -0.39 to 0.39; $p = 1.00$) in corneal staining scores, measured using the Oxford scale, between Ramadan fasting and non-fasting periods.

The GRADE certainty of the evidence for each of these outcomes (TBUT, Schirmer score, tear osmolarity, and corneal staining score) was judged as very low (Table 5).

1. Bariatric surgery

Four studies investigated bariatric surgery using pre-post [503, 669, 670] or retrospective cohort study designs [504]. Together they enrolled 161 participants; individual sample sizes ranged 20 to 89 participants [503, 504]. The pre-post intervention studies evaluated the outcome measures at baseline and 12-months after bariatric surgery. The retrospective cohort study compared pre-operative with post-bariatric surgery groups consisting of between 1-12

months post-surgery, and greater than 12-months. Of the four included studies, three [503, 669, 670] did not measure any of the primary or secondary outcomes.

Primary outcome

One study [504] provided very low certainty evidence (Table 5) for no significant difference in OSDI scores between pre-operative group, and in another group who were at least 12-months post-bariatric surgery (57 participants; mean difference: 8.30 units; CI: -4.79 to 21.39; $p = 0.21$).

Secondary outcomes

There was no difference in fluorescein TBUT in one study measured in separate groups pre-operatively and greater than 12-months post bariatric surgery (57 participants; mean difference: -0.20 CI: -2.88 to 2.48; $p = 0.88$) [504]. This study also reported no difference in Schirmer scores measured without anaesthesia (57 participants; mean difference: 2.40 mm/5 min; CI: -4.41 to 9.21; $p = 0.49$) between the study groups. The certainty of the evidence for both outcomes was judged as very low (Table 5).

2. Anorexia nervosa

Four studies evaluated participants with anorexia nervosa compared to healthy controls using a cross-sectional design [295, 659, 671, 674]. Combined, these studies included 152 participants; sample sizes ranged from 14 to 76 participants. Only one [3] of the four studies reported data on Schirmer scores. None of the studies reported data on the primary or other secondary outcomes.

One study [659] provided very low certainty evidence (Table 5) for lower Schirmer scores measured with anaesthesia in an anorexia nervosa group compared to healthy controls (14 participants; mean difference: -11.10 mm/5 min; CI: -16.76 to -5.44; $p < 0.001$).

Table 5: Summary of findings, including Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessments for the certainty of the body of evidence, for religious fasting, bariatric surgery, and anorexia nervosa.

Intervention/exposure vs comparator	Outcome measure	No. of participants (no. of studies)	Certainty of the evidence (GRADE)	Estimated (CI)
				with intervention/exposure
Pre versus post Ramadan fasting	Dry eye symptom score, measured using a questionnaire or rating scale	79 (2)	⊕⊖⊖⊖ ^a Very low	Study #1 [336] reported significantly higher symptom scores with Ramadan fasting compared to non-fasting: 5.60 units higher (1.84 lower to 9.36 higher). Study #2 [339] reported no significant difference in symptom scores measured with Ramadan fasting compared to non-fasting: MD: 4.50 units lower (13.07 lower to 4.07 higher). Both studies [336, 339] measured dry eye symptoms using the OSDI questionnaire .
	Tear film break up time (s), measured using non-invasive or sodium fluorescein method	205 (4)	⊕⊖⊖⊖ ^b Very low	Study #1 [339] reported significantly lower tear break up time with Ramadan fasting compared to non-fasting: MD: -1.7 seconds lower (2.93 lower to 0.47 higher). Study #2 [337] reported no significant difference between Ramadan fasting versus non-fasting: MD: 1.46 higher (0.34 lower to 3.26 higher). Study #3 [336] reported no significant difference between Ramadan fasting versus non-fasting: MD: 0.80 lower (1.66 lower to 0.06 higher). Study #4 [338] reported no significant difference between morning versus evening of Ramadan fasting: MD: 3.55 seconds higher (1.64 lower to 8.74 higher).

				Three studies [336, 338, 339] used a sodium fluorescein method and one study [33] used a non-invasive method.
Tear volume/flow (mm/5 minutes), measured using the Schirmer score	142 (4)	⊕⊕⊕⊕ ^c Very low		<p>Study #1 [336] reported significantly lower Schirmer score with Ramadan fasting compared to non-fasting: MD: 4.20 mm/5 min lower (6.43 lower to 1.97 higher).</p> <p>Study #2 [676] reported no significant difference between Ramadan fasting versus non-fasting: MD: 0.26 mm/5 min lower (2.16 lower to 1.64 higher).</p> <p>Study #3 [339] reported no significant difference between Ramadan fasting versus non-fasting: MD: 0.90 mm/5 min lower (2.88 lower to 1.08 higher).</p> <p>Study #4 [338] reported no significant difference between morning versus evening of Ramadan fasting: MD: 0.20 mm/5 min lower (3.34 lower to 2.94 higher).</p> <p>Measurement techniques involved - two studies with anaesthesia [338, 339], one study without anaesthesia [336], and another study using both with/without anaesthesia [676].</p>
Corneal staining score, measured using a grading scale	50 (1)	⊕⊕⊕⊕ ^d Very low		One study [339] reported no significant difference between Ramadan fasting versus non-fasting: MD: 0.00 units (0.39 lower to 0.39 higher). This study used Oxford grading scale to quantify corneal staining.
Tear osmolarity (mOsm/L)	29 (1)	⊕⊕⊕⊕ ^e Very low		One study [336] found a significantly higher tear osmolarity during Ramadan fasting compared to a non-fasting period: 7.70 mOsm/L higher (1.58 lower to 13.82 higher).

				In this study tear osmolarity was measured using the OcuSense TearLab system.
Pre-operative versus post-bariatric surgery	Dry eye symptom score, measured using a questionnaire or rating scale	57 (1)	⊕⊕⊕⊕ ^f Very low	One study [504] found no significant difference between measures in a pre-operative group, and in another group who were at least 12-months post bariatric surgery: MD: 8.30 units higher (4.79 lower to 21.39 higher). This study measured dry eye symptoms using the OSDI questionnaire.
	Tear film break up time (s), measured using sodium fluorescein method	57 (1)	⊕⊕⊕⊕ ^f Very low	One study [504] found no significant difference between pre-operative versus greater than 12-months post-surgery groups: MD: 0.20 seconds lower (2.88 lower to 2.48 higher).
	Tear volume/flow (mm/5 minutes), measured using the Schirmer score	57 (1)	⊕⊕⊕⊕ ^f Very low	One study [504] found no significant difference between pre-operative versus greater than 12-months post-surgery groups: MD: 2.40 mm/5 min (4.41 lower to 9.21 higher). This study measured Schirmer score without anaesthesia.
Anorexia nervosa versus healthy controls	Tear volume/flow (mm/5 minutes), measured using the Schirmer score	14 (1)	⊕⊕⊕⊕ ^g Very low	One study [659] found a significantly lower score in the anorexia nervosa group compared to controls: MD: 11.10 mm/5 min lower (16.76 lower to 5.44 higher). This study measured Schirmer score with anaesthesia.

Abbreviations: CI, confidence interval; MD, mean difference; mm, millimetre; min, minutes; OSDI, ocular surface disease index. *Only outcome measures evaluated by at least one study are listed.

^aDowngraded two levels due to risk of bias as all four studies were judged to be of poor quality (refer supplement I for details) [336, 339].

^bDowngraded three levels due to risk of bias as all four studies were judged to be of poor quality (refer supplement I for details) [336-339, 676].

^cDowngraded three levels due to risk of bias as all four studies were judged to be of poor quality (refer supplement I for details) [336, 338, 339, 676].

^dDowngraded three levels due to imprecision, as outcome data derived from one study [339] with a small sample size.

^eDowngraded three levels due to imprecision, as outcome data derived from one study [336] with a small sample size.

^fDowngraded three levels due to imprecision, as outcome data derived from one study [504] with a small sample size.

^gDowngraded three levels due to imprecision, as outcome data derived from [659] with a small sample size.

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Table 6: Key characteristics of the included studies

Study	Intervention/condition	Study design	Research question type	Study location	Total sample size (No of female)	Participant age (years)		Ocular surface outcomes measured	Overall study quality based on RoB judgements [^]
						Intervention/condition Mean (SD)	Comparator Mean (SD)		
Armstrong et al. (2019) [339]	Religious fasting - Ramadan	Pre-post	Intervention	UAE	50 (27)	32 [R: 23 to 45]		1) OSDI score 2) Schirmer score - with anaesthesia 3) Fluorescein TBUT 4) Corneal staining score 5) Inflammation Dry	(1) Poor
Baser et al. (2016) [672]		Pre-post	Intervention	NR	15 (0)	34.13 (7.74)		1) CCT	(2) Poor

Beyoglu et al. (2020) [673]		Cross-sectional	Aetiology	Turkey	100 (47)	34.96 (16.01)	36.06 (14.28)	1) Corneal endothelial cell density 2) CCT	(3) Poor
Kayikcioglu et al. (1998) [338]		Pre-post	Intervention	NR	32 (0)	22.3 (2.9)		1) Schirmer score – with anaesthesia 2) Fluorescein TBUT	(4) Poor
Kerimoglu et al. (2010) [676]		Pre-post	Intervention	NR	31(12)	31.7 (5.3)		1) Schirmer score – both with/without anaesthesia 2) CCT	(5) Poor
Koktekir et al. (2014) [336]		Pre-post	Intervention	NR	29 (0)	27.8 (5.9)		1) OSDI score 2) Schirmer score – without anaesthesia 3) Fluorescein TBUT 4) Corneal and	(6) Poor

								conjunctival staining 5) Tear osmolarity	
Nilforushan et al. (2020) [677]		Pre-post	Intervention	NR	27 (17)	40.07 (9.29)		1) CCT	(7) Poor
Nowroozadeh et al. (2012) [678]		Pre-post	Intervention	NR	22 (10)	60.55 (12.20)		1) Keratometry 2) Corneal astigmatism 3) Corneal radii of curvature	(8) Poor
Oltulu et al. (2016) [679]		Cross-sectional	Aetiology	NR	134 (NR)	31.4 (9.3)	30.2 (10.7)	1) Corneal hysteresis 2) Corneal resistance factor	(9) Poor
Sarici et al. (2016) [681]		Pre-post	Intervention	Turkey	29 (NR)	38.07 (10.18)		1) CCT 2) Corneal astigmatism 3) Corneal volume 3) Corneal hysteresis	(10) Poor

								4) Corneal resistance factor	
Sariri et al. (2010) [335]		Pre-post	Intervention	NR	60 (25)	R: 23 to 27		1) Ocular tear protein levels	(11)Poor
Sedaghat et al. (2017) [337]		Pre-post	Intervention	Iran	94 (40)	35.12 (9.07)		1) CCT 2) NIKBUT	(12)Poor
Selver et al. (2017) [682]		Prospective cohort	Aetiology	NR	61 (35)	43.35 (13.20)	43.17 (12.90)	1) CCT	(13)Unsatisfactory
Uysal et al. (2018) [683]		Pre-post	Intervention	NR	41(0)	32.7 (5.1)		1) CCT 2) Corneal hysteresis 3) Corneal resistance factor 4) Corneal volume	(14)Poor
Rocha et al. (2002) [680]	12-hours fasting	Cross-sectional	Aetiology	NR	33 (16)	R: 23 to 51		1) Insulin levels in tears	(15)Poor
Adam et al. (2021) [669]	Bariatric surgery	Pre-post	Intervention	UK	26 (16)	52 (10)		1) Corneal nerve fibre density 2) Corneal branch density	(16)Fair

								3) Corneal fibre length	
Azmi et al. (2021) [670]		Pre-post	Intervention	UK	26 (17)	46.23 (8.6)		1) Corneal nerve fibre density 2) Corneal branch density 3) Corneal fibre length	(17)Poor
Iqbal et al. (2021) [503]		Pre-post	Intervention	UK	20 (NR)	48.8 (8.3)		1) Corneal nerve fibre density 2) Corneal branch density 3) Corneal fibre length 4) Keratocyte density	(18)Poor
Marques et al. (2017) [504]		Retrospective cohort	Aetiology	Brazil	89 (81)	46.5 (7.3)	41.3 (9.3)	1) OSDI score 2) Schirmer score - without anaesthesia	(19)Unsatisfactory

								3) Fluorescein TBUT 4) Rose Bengal staining score 5) Tear ferning test 6) Conjunctival impression cytology	
Abraham et al. (1980) [295]	Anorexia nervosa	Cross-sectional	Aetiology	NR	26 (26)	22 [R: 15 to 22]	R: 18 to 22	1) Anterior segment evaluation using slit lamp biomicroscopy	(20)Poor
Barbato et al. (2006) [671]		Cross-sectional	Aetiology	NR	36 (36)	20.1 (4.3)	20.3 (1.3)	1) Blink rate	(21)Poor
Frank et al. (2020) [674]		Cross-sectional	Aetiology	NR	76 (76)	22.61 (7.27)	23.27 (5.35)	1) Blink rate	(22)Poor
Gilbert et al. (1990) [659]		Cross-sectional	Aetiology	USA	14 (14)	22 [NR]	24.6 [NR]	1) Anterior segment evaluation using slit lamp	(23)Poor

								biomicroscopy 2) Schirmer score - with anaesthesia 3) Conjunctival impression cytology	
Donmez Gun et al. (2021) [613]	Celiac disease	Cross-sectional	Aetiology	Turkey	71 (51)	39.56 (7.39)	36.34 (7.62)	1) CCT 2) Corneal endothelial cell density	(24)Poor
Hills et al. (1951) [675]	Riboflavin depletion	Non-RCT	Intervention	USA	39 (0)	R: 18 to 48		1) Anterior segment evaluation using slit lamp biomicroscopy 2) Schirmer score – technique not reported 3) Corneal sensitivity	(25)Serious concerns

Abbreviations: CCT, central corneal thickness; NR, not reported; NIKBUT, non-invasive keratograph breakup time; OSDI, ocular surface disease index, R, range; RCT, randomized controlled trial; RoB, risk of bias; SD, standard deviation; TBUT, tear break up time; UAE, United Arab Emirates. ^Assessments were performed using the relevant risk of bias tools, which were: ROBINS-I tool for non-RCT [9], Newcastle Ottawa scale for cohort and case-control studies [10], NIH tool for both cross-sectional, and pre-post studies with no control group [11].

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3. Short-term (12-hour) fasting

One study [680] investigated the effect of a 12-hour fasting period compared to a non-fasting group using a cross-sectional design. In total, 33 participants were evaluated but the study did not measure any of the primary or secondary outcomes.

4. Celiac disease

Participants with Celiac disease were compared to healthy controls using a cross-sectional study design [613]. This study included 71 participants, but did not measure any of the primary or secondary outcomes.

5. Riboflavin depletion diet

An investigation of the effect of riboflavin depletion diet compared to a normal unrestricted diet in 39 participants using a non-randomized controlled trial design did not measure any of the primary or secondary outcomes [22].

6.4 Discussion

This is the first systematic review to investigate the effects of intentional food restriction on ocular surface health. Of the 25 included studies, most investigated Ramadan fasting (56%), followed by bariatric surgery (16%), anorexia nervosa (16%), or other interventions/conditions (12%), which included 12-hour fasting, celiac disease and riboflavin depletion diet. Based on risk of bias assessments, none of the studies were judged to be of high quality (i.e., at minimal risk of bias). All studies were assessed to be of fair, poor or unsatisfactory quality or having serious risk of bias, as determined by the appropriate risk of bias tool for the study design. Common reasons for downgrading the quality assessments were lack of masking of the investigator/outcome assessor(s) and failure to report the sample size calculations. The

GRADE certainty of the evidence for the pre-specified primary and secondary outcomes, across all interventions, was judged as very low.

This review did not identify any relevant studies that used a randomized controlled trial design; most studies were of a pre-post intervention design (56%).-The National Health and Medical Research Council of Australia evidence hierarchy proposed that studies with pre-post designs contribute a relatively low level of empirical evidence for intervention questions (Level IV) [684]; this acknowledges the inherent limitations and risk of bias in these designs, which include lack of randomisation, potential for regression to the mean and poor internal validity. These limitations should be considered when interpreting the individual study results in this review. To build upon the current evidence base, future studies should consider the benefits of randomized controlled trial designs, where possible, in minimising risks of bias, to enable greater certainty to be achieved in understanding the effect of intentional food restriction on ocular surface parameters. However, it is acknowledged that it is generally unethical to delay or randomise religious fasting, dieting or weight loss surgery; so the current evidence may continue to be the best available to inform decision making.

In this review, no studies were found to mask both participants and outcome assessors. This finding is not surprising given the clear challenges associated with masking participants (in particular) for interventions that include religious fasting, dietary restriction and surgery. There is also the possibility that treatment effects or adverse events associated with particular surgeries or diets might (inadvertently) unmask outcome assessors. For interventions where participants and/or outcome assessors are unable to be masked, attempts should be made to minimise other sources of bias. For example, this might include measures to uniform the delivery of intervention(s), equivalent follow-up period between the study groups and the selection of objective outcome measures, where possible, to reduce the potential influence of participant or outcome assessor input that might induce measurement bias [685].

Of the 25 included studies, none reported adverse event data. This limits the investigation of the safety of intentional food restrictions on the ocular surface, or the opportunity to conduct risk-benefit analysis. Hence, future studies should comprehensively assess and report adverse events to enable a more complete understanding of the safety profile of intentional food restriction in relation to the ocular surface.

7 CONCLUSIONS AND NEW FRONTIERS

Nutrition is a modifiable factor that can influence general health and well-being. This report explored the various aspects of nutrition and the evidence relating to its impact on the health of the ocular surface. An overarching issue identified is the relative paucity of high-quality evidence in explaining the role of nutrition in ocular surface health and disease. A summary of the evidence found is highlighted in Table 7 and Figure 5.

Table 7: The current evidence relating to nutrition and ocular surface health . (+): the item has been associated with a positive effect on ocular surface health; (-) the item has been associated with a negative effect on ocular surface health; (±): The item has been associated with both positive and negative effects on ocular surface health

Topic area	Conclusive ^a	Probable ^b	Inconclusive ^c
Key elements of nutrition linked to ocular surface disease	Vitamin A deficiency (-) Vitamin C deficiency (-)	Vitamin B ₁₂ deficiency (-) Vitamin D deficiency (-) Omega 6:3 imbalance (omega 6 (-), omega 3(+))	Sugars and artificial sweeteners (-) Gluten (-) Hydration (+) Selenium (+) Lactoferrin (+)
Excipients, additives and non-nutritional components linked to ocular surface disease		Mercury (-)	Bisphenol A (-) Phthalates (-) Alcohol (-)
Dietary supplements studied relative to their ability to improve the status of ocular health	Omega 3 (+) Vitamin A (+)	Curcumin (+) Vitamin B ₁₂ (+) Probiotics and prebiotics (+)	Caffeine (+) Collagen (+) Chinese Herbs (+) Honey (+) Selenium (+) Seeds (+)
Eating disorders, food intolerance, allergy, and different diets linked to ocular surface disease	Food allergy (-)	Anorexia nervosa (-) Mediterranean diet (+) Bariatric surgery (-)	Bulimia nervosa (-) Food intolerance (-) Western diet (-) African diet (+) Asian diet(+) Food restriction diets (±)
Gut microbiome aspects linked to ocular surface disease		Gut dysbiosis (-)	
Nutrition-related systemic disease linked to ocular surface disease	Obesity (-) Pre-diabetes and type 2 diabetes (-) Gastrointestinal disease (-)	Dyslipidemia (-) Hypertension (±) Metabolic syndrome (-) Cardiovascular disease (-) Chronic kidney disease (-)	Cancer (-)

^a Consistent evidence implies the existence of at least one adequately powered and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biological rationale and corroborating basic research or clinical data. ^b Suggestive evidence implies the existence of either inconclusive information from peer-reviewed publications or inconclusive or limited information to support the association, but either not published or published somewhere other than in a peer-reviewed journal.

^c Inconclusive evidence implies either directly conflicting information in peer-reviewed publications, or inconclusive information but with some basis for a biological rationale.

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With regards to macronutrients, evidence that omega-3 deficiency results in ocular surface sequelae is provided in accumulating (though sometimes conflicting) evidence, particularly with regard to dry eye disease. Direct evidence, however, is lacking for the role of oils such as olive oil, primrose oil, palm oil, soybean oil and hydrogenated vegetable oils. Sugars and artificial sweeteners, while being shown to be involved in metabolic syndrome and glucose intolerance, have not yet been studied with regard to the ocular surface. Similarly, although gluten-free diets have been adopted in those with celiac disease, and ocular surface inflammation can develop in these individuals, eliminating gluten from the diet has not been studied with respect to ocular surface inflammation.

In regard to micronutrients, the major vitamins identified to play a role in ocular surface health are vitamins A, B₁₂, C and D. Particularly, deficiencies have been associated with ocular surface disease.

Dietary supplements were explored. Based on the current evidence, caffeine use does not appear to be a risk factor for dry eye disease and may have beneficial effects on tear production and symptoms, but further research is needed to verify these findings. Studies on collagen, oral honey and seeds, and their effect on the ocular surface are limited, while studies on various herbs and spices tend to indicate improved dry eye parameters but lack high-quality evidence. Minerals in dry eye have been explored only in conjunction with vitamins, anti-oxidants and/or omega-3-fatty acids, and so their sole effect on the ocular surface needs to be examined. Two separate meta-analyses of studies examining selenium intake in individuals with Graves ophthalmopathy concluded that the evidence does not yet support a role for selenium supplementation in standard care of auto-immune thyroiditis, with a possible exception for persons with a known selenium deficiency.

Omega-3 and omega-6 polyunsaturated fatty acids are the most extensively studied dietary supplements in ocular surface disease, with numerous randomized controlled trials and

systematic reviews and meta-analyses, mostly in patients with dry eye disease or MGD. Given the current evidence of efficacy and their relatively favorable safety profile, omega-3 fatty acids may be a relevant treatment option for patients with dry eye disease and MGD, acknowledging that their exact role in treatment remains incompletely understood. A recommendation for future studies is that baseline measurements of omega-3 status are reported using surveys of food-intake as a surrogate measure of blood levels of omega-3. Future studies should also determine if, and possibly which, dry eye patient subgroup(s) (subtype and/or severity of dry eye, or those who are omega-3 deficient) may benefit most from supplementation, whether a certain form or composition of omega-3 is preferable, what dosage and duration is best to recommend, and what dietary ratio of omega-3 to -6 is optimal for dry eye. Appropriate sample size calculation, prospective trial registration, provision of details regarding the polyunsaturated fatty acids intervention including form and best practice for inclusion criteria for dry eye are key recommendations for these studies.

Hydration is essential for the optimal function of the human body including physical and cognitive performance. However, to date there have been few studies that assessed the role of hydration status or water intake on ocular surface health. Future longitudinal studies should investigate whether increasing water intake is beneficial in patients with dry eye disease.

An area of increasing interest is that of the role of excipients, additives and non-nutritional components on health. Further studies on the role of the many endocrine-disrupting chemicals on ocular surface disease are clearly needed, as well as the possible effects of food additives and non-nutritional chemicals, such as nanoparticles, emulsifiers and flavor enhancers, including glutaminase and monosodium glutamate, with most studies to-date being directed at their impact on systemic health and the gut microbiome. Mercury, most commonly consumed in mercury-contaminated seafood, has been linked to greater ocular surface discomfort, as has alcohol.

The concept of whole foods versus vitamin extracts, highlighting the complexes of macronutrients, micronutrients, bioactive compounds, and their concomitant interactions contained within whole foods, and the challenge of identifying the effects of single dietary nutrients, within or outside the context of the overall diet. There is a paucity of data on the effect of different diets, with the effect of a high-fat diet, reflective of the Western diet, being largely explored in animal models. The Mediterranean diet is the most studied, with interventional studies providing conflicting data with regard to the impact on dry eye parameters. Further research is needed to explore the impact of various diets and nutrients on the ocular surface including a better understanding of absorption on the surface.. Changing diet through acculturation might offer more understanding of impact of different diets on ocular surface disease.

The Subcommittee undertook a systematic review and meta-analysis to evaluate the effects of intentional food restriction on the ocular surface, concluding that there was a lack of high-quality evidence assessing this question to-date. Mixed results were reported in individual studies in relation to the effects of religious fasting and bariatric surgery on traditional measures of ocular surface health (for example, dry eye symptoms, TBUT and Schirmer score). Whether intentional food restriction affects the health of the surface of the eye therefore remains unclear.

Investigations into the gut microbiome and the ocular surface have been limited in size and sporadic, and much can be learned from additional research in this area. There is little evidence currently to state definitively that modulation of the gut microbiome can have beneficial effects on the ocular surface. Many metabolic and gastrointestinal disorders have been associated with an increased risk of ocular surface disease. Although the exact pathophysiological pathways leading to comorbid ocular surface diseases are often unknown for these disorders, the disorders may lead to deficiencies of micro- and macronutrients that are important in

maintaining ocular surface health. With respect to cancer, most potential impacts on the ocular surface are likely to be overshadowed by the side-effects of chemotherapy.

The role of epigenetics in ocular surface disease is not well explored, although emerging evidence suggests that epigenetic modification may play a role in ocular surface diseases such as pterygium and keratitis.

In general, better-quality evidence is required in most of the areas covered in this report, including studies with adequate power. Future studies on dietary supplements should report on factors such as dosage and compare to a control group as well as baseline measures. Moreover, future studies should also consider the broader dietary intake of study participants and any changes that occur over the course of the study and any adverse events that arise during the study. Future studies will also aid in our understanding of the role of biomarkers that can detect nutritional deficiencies and hence prevent nutrition-related ocular surface disease.

Good nutrition is clearly pivotal to good health. There is significant evidence that good nutrition also impacts the ocular surface. Our journey to understanding the role of nutrition in every aspect of ocular surface health is still in its relative infancy, although progress is being made in many areas. Eyecare professionals are advised to consider the evidence prior to providing nutritional recommendations to patients with regard to their ocular surface health. Similarly, they would be advised to consider a patient's food habits in general, especially in patients with severe dry eye disease, and to consider co-management with dietitians.

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FIGURES

Figure 1: Flow diagram of studies included in the systematic review in section 6.

Figure 2: Forest plot of comparison: Ramadan fasting vs. control (non-fasting).

Outcome: Dry eye symptoms measured using the OSDI questionnaire. For Koktekir et al.[336] it is unclear if there were any losses to follow-up; an assumption was made that all participants that were initially recruited (n = 29) completed the study. Higher scores indicate more severe symptoms.

Figure 3: Forest plot of comparison: Ramadan fasting vs. control (non-fasting).

Outcome: TBUT, measured in seconds. For Koktekir et al.[336], Kayikcioglu et al.[338], and Sedaghat et al.[337] it was unclear if there were any losses to follow-up; an assumption was made that all participants that were initially recruited completed the study. Higher scores indicate greater tear film stability.

Figure 4: Forest plot of comparison: Ramadan fasting vs. control (non-fasting).

Outcome: Tear volume/flow measured using the Schirmer score (mm/5 minute). For Koktekir et al.[336], Kayikcioglu et al.[338], and Kerimoglu et al.[676] it was unclear if there were any losses to follow-up; an assumption was made that all participants that were initially recruited completed the study. Higher scores indicate greater tear production.

Figure 5: The impact of nutrition on the ocular surface. Summary of the possible positive and negative impact on the ocular surface.

SUPPLEMENTARY MATERIAL

Supplementary Material for systematic review (section 6) entitled “The effect(s) of different forms of intentional food restriction on the ocular surface: a systematic review and meta-analysis”

Table S1: Reasons for excluding studies at the full-text screening stage

Table S2: Assessment of risk of bias in included pre-post intervention studies, for each domain in the NIH pre-post intervention tool

Table S3: Assessment of risk of bias in included cross-sectional intervention studies, for each domain in the NIH cross-sectional intervention tool

Table S4: Assessment of risk of bias in included non-randomised experimental study, for each domain in the ROBINS-1 tool

Table S5: Assessment of risk of bias in included cohort studies, for each domain in the Newcastle-Ottawa Quality Assessment for Cohort studies tool.

Appendix SI: Search strategies

Figure 1

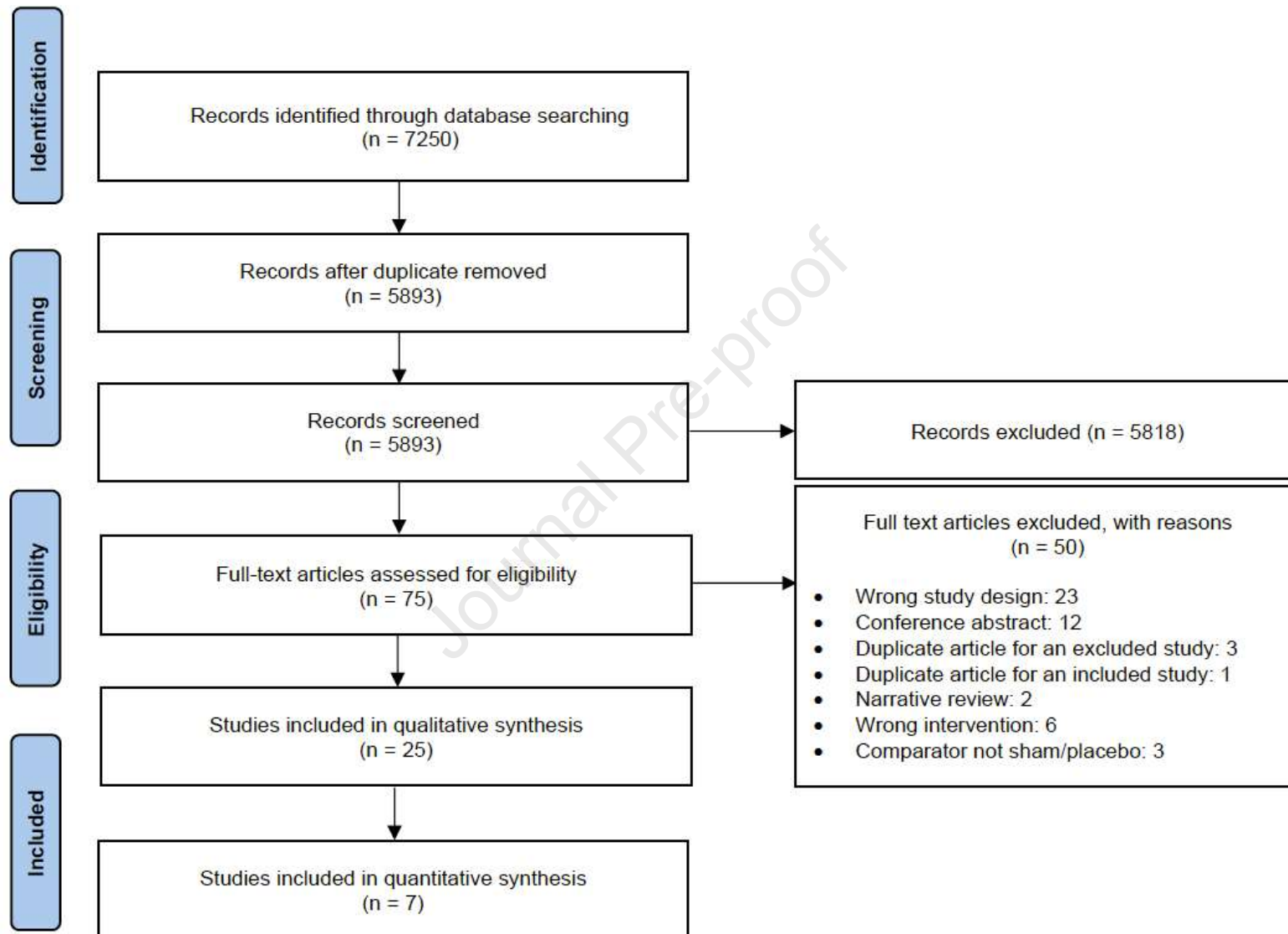


Figure 2

Ramadan fasting - Dry eye symptom score

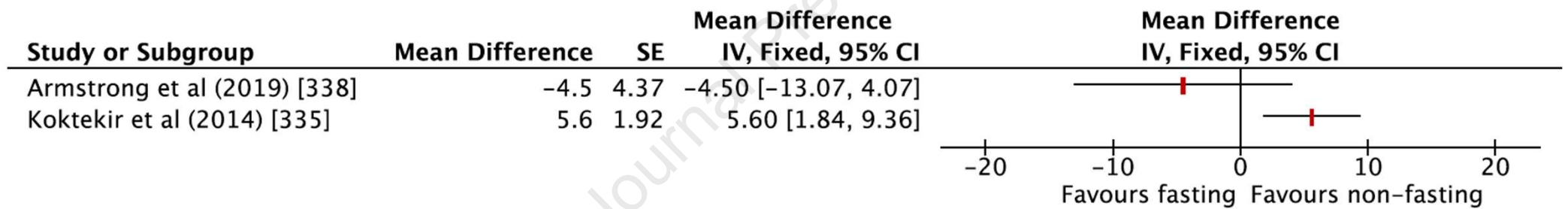


Figure 3

Ramadan fasting - Tear break up time (s)

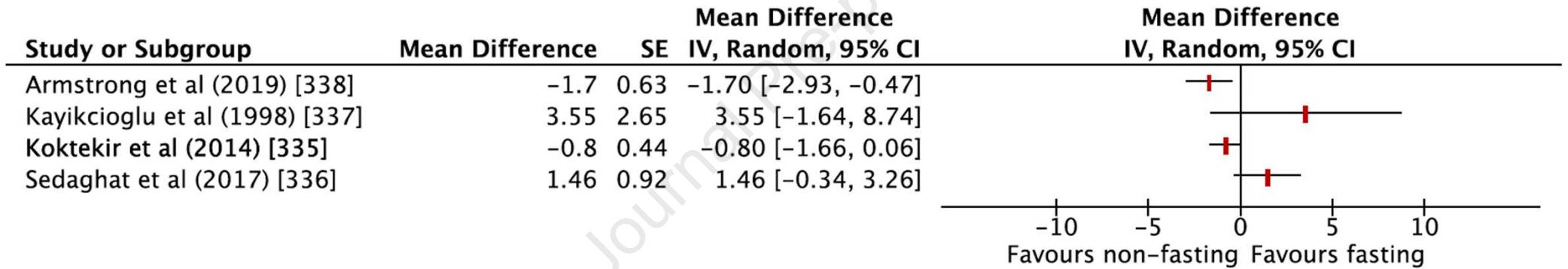


Figure 4

Ramadan fasting - Schirmer test score (mm)

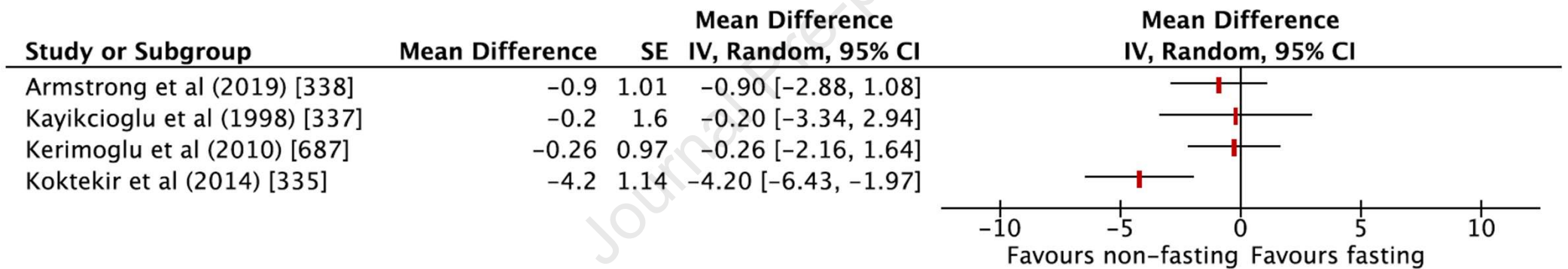


Figure 5

