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Optimizing Atopic Dermatitis Management: Insight into Dietary and Lifestyle Interventions

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Abstract

Atopic dermatitis (AD) is a prevalent, chronic inflammatory skin condition that significantly affects patients' quality of life. Current treatments in most parts of the world typically include topical corticosteroids (TCS) and other immune-modulating or suppressing drugs, which can often have adverse effects. Since patients are often not offered alternative solutions to manage their AD, misuse of TCS in hopes of symptom relief prevails. This review aims to consolidate and evaluate the current literature on non-pharmaceutical interventions for managing AD, focusing on dietary adjustments, intake of various nutrients and nutraceuticals, the external environment, and lifestyle factors such as sleep and stress. Dietary approaches emphasize an anti-inflammatory diet with avoidance of trigger foods, as well as intake of nutrients such as omega-3 polyunsaturated acids (n-3 PUFAs), polyphenols, vitamins D and E, and zinc. Probiotics are useful in diversifying the gut microbiome, which can contribute to reducing systemic inflammation. The external environment also plays a role, with urban environments leading to heightened AD incidence and climate factors also being influential. High-quality sleep and stress management techniques are key for mitigating flares and helping patients. Other alternative complimentary modalities such as herbal remedies and acupuncture have been used for centuries to help manage and treat AD, offering a unique perspective of the condition. By highlighting a more holistic approach, this review seeks to empower patients to consider a number of factors that should be considered in crafting their personalized AD treatment approach, offering a comprehensive framework for understanding how an integrative approach can be effectively utilized.

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Chapter I: Introduction

I.1. Symptoms and Pathology

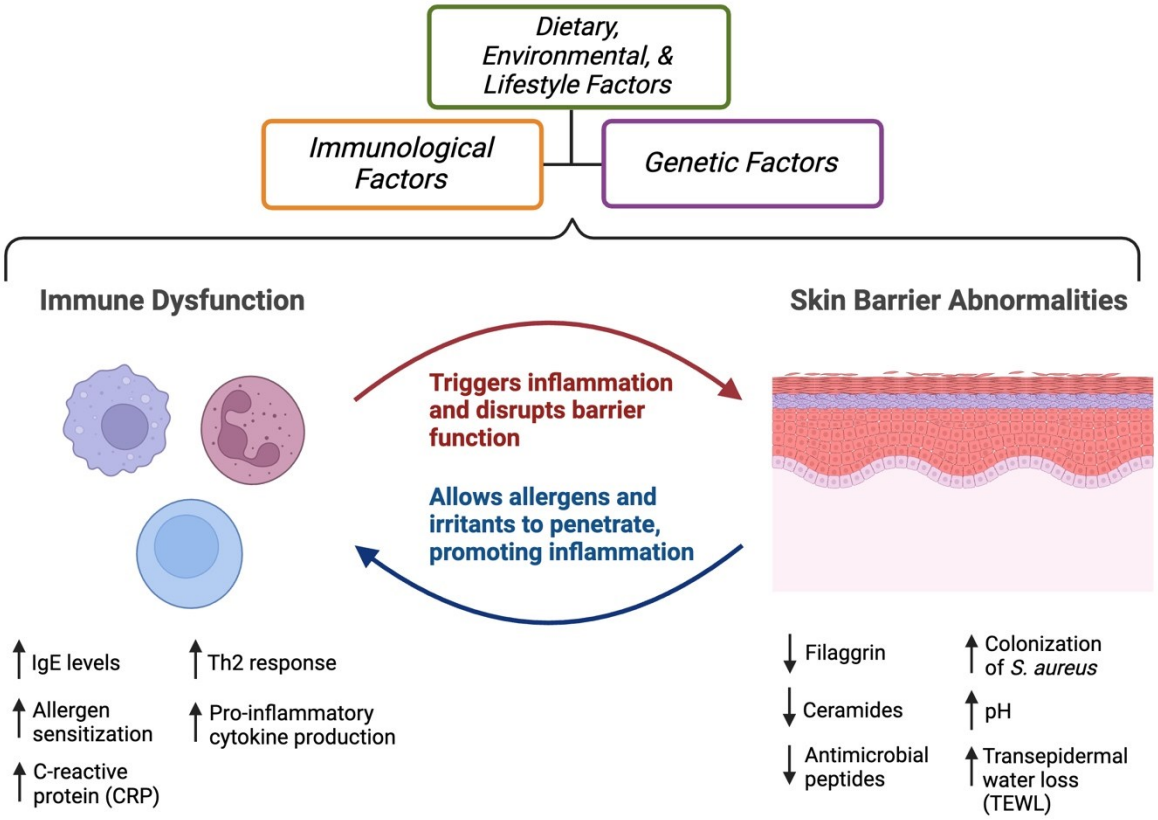
Atopic dermatitis (AD), also known as eczema, is a chronic and complex inflammatory skin condition characterized by redness, dryness, intense itching (pruritus), and recurrent eczematous lesions. It is extremely common among both children and adults, making it a leading non-fatal health burden across the world. The chronicity of the disease can be extremely challenging and includes periods of remissions and flares. While non-fatal, the often misunderstood and underplayed condition inflicts significant psychological and psychosocial burden onto patients of all ages, negatively impacting quality of life (Weidinger & Novak, 2016). The disease involves a wide array of genetic, environmental, and immunological factors, which are believed to be highly interconnected, furthering the complexity involved in diagnosis and treatment (Eyerich et al., 2018). These various factors lead to the two key components of AD pathogenesis– immune dysfunction and skin barrier abnormalities (Yang et al., 2020).

In terms of immune dysfunction, AD involves an increase in serum immunoglobulin E (IgE) levels, sensitization of allergens, and predominance of Th2 cytokines (Yang et al., 2020). The activation of immune cells via cytokine production and their migration to the skin play an essential role in AD, which in turn, might result in higher susceptibility of the skin to environmental factors (Werfel et al., 2016). Moreover, research has found that AD patients tend to have significantly increased C-reactive protein (CRP) levels when compared to healthy controls, and that these findings serve as a marker for disease severity in moderate-to-severe AD patients (Vekaria et al., 2017). Interestingly, other studies have found that CRP levels are increased in adult chronic AD patients but not in children and adolescents with active AD. These facts support the idea that chronic AD has a substantial systemic inflammatory component (Silverberg, 2015; Wang et al., 2017). When discussing immune dysfunction in AD, it is important to note that in addition to the symptoms created within the condition itself, AD can also increase the risk for IgE-mediated food allergy, asthma, and allergic rhinitis– a concept known as atopic march (Hill & Spergel, 2018). Atopic march suggests that the presence of one allergic condition increases the risk for the development of others, with atopic dermatitis as the typical starting point– further highlighting the fact that AD is not an isolated condition, but rather part of a much larger cascade (Hill et al., 2016).

The skin barrier, which is considered the first host defense mechanism against microbiomes and allergens, plays an extremely important role, as its expression often represents a part of the innate immune system (Yang et al., 2020). In understanding its

functionality, it is clear how AD may manifest when the skin barrier is compromised. Some major contributors to the pathogenesis of skin barrier abnormalities include decreased filaggrin, ceramides, and antimicrobial peptides (Zaniboni et al., 2016). Of particular interest in recent research, filaggrin is a major epidermal protein that has been shown to play a key role in the pathogenesis of AD. A deficiency of this protein is found in up to 60% of patients with AD (Palmer et al., 2006). While considered a genetic component, it is influenceable by external and environmental mechanisms (Drislane & Irvine, 2020). Another hallmark of skin barrier disruption in AD is increased skin pH and microbiome dysbiosis, specifically for colonization and overgrowth by microbial organisms such as Staphylococcus aureus (*S. aureus*) and herpes simplex virus (Boguniewicz & Leung, 2011; Hülpüsch et al., 2021). The interplay between immune dysfunction and compromised skin barrier highlights the complex nature of AD, however, intrinsic factors such as these do not encompass the whole story. The current review will rather focus more so on extrinsic factors, such as those which may be controlled via diet, environment, and lifestyle factors in order to mitigate or improve AD (*Figure 1*). Of course, there is an interplay of extrinsic and intrinsic factors where one certainly affects the other, however, in highlighting the importance of the extrinsic, this review serves to show readers and patients that they can have control over their condition through various lifestyle aspects. After all, genetics may load the gun, but lifestyle pulls the trigger.

Figure 1. *Factors influencing AD and its pathogenesis.*

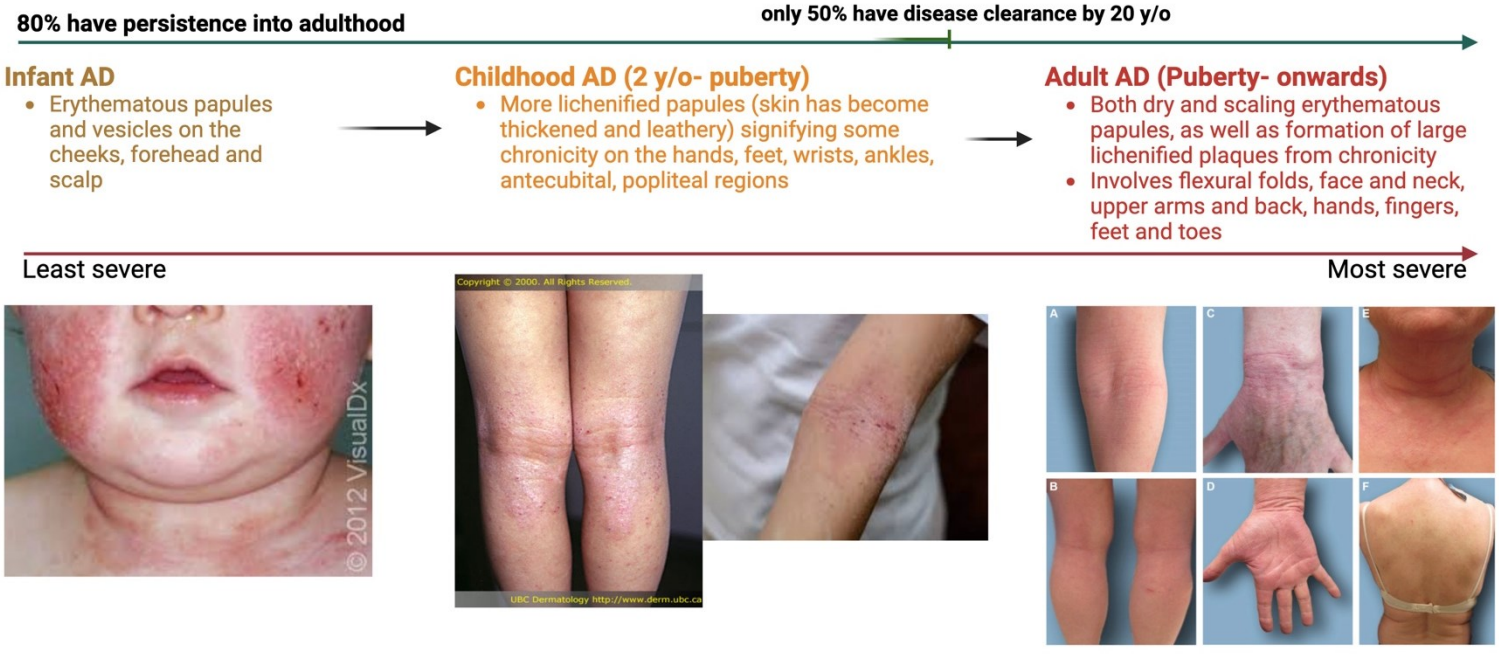


I.2. AD in Children vs. Adults

Before delving into these external influences, it is crucial to grasp the disease's progression and its varied classifications based on age. While early literature focused more on the condition during childhood, newer studies have suggested significant prevalence of AD in adult populations (Silverberg, 2019). While onset during childhood may be more frequent, persistence into adulthood often reflects the more severe cases of AD, making it increasingly important to understand (Hanifin, 2017). Notably, one longitudinal study found that 80% of children have persistence of AD symptoms into adulthood, with only 50% achieving a period of disease clearance or decrease by 20 years of age (Margolis et al., 2014). In addition to childhood AD that persists into adulthood, there also exists adult-onset AD, which is perhaps the least understood and complicated variant of the condition (Ozkaya, 2005). The clinical pattern of AD varies with age and can typically be grouped into three categories– infant, childhood (2 years old to puberty), and adulthood (puberty onwards). Infants usually present

with erythematous (reddened) papules and vesicles on the cheeks, forehead, and scalp. Children, on the other hand, often exhibit more lichenified papules (meaning the skin has become thickened and leathery), signifying chronicity of the disease on the hands, feet, wrists, ankles, antecubital, and popliteal regions. Finally, adult AD typically involves the flexural folds, face and neck, upper arms and back, hands, fingers, feet, and toes. For adults, typical manifestation includes both dry, scaling erythematous papules as well as the formation of large lichenified plaques from chronicity (Akdis et al., 2006). Most commonly, adult-onset AD notoriously associated with symptomatic head, neck, and hand areas (Silverberg et al., 2018). This information can be seen in *Figure 2*. Disturbingly, one study comparing adult patients with either child-onset or adult-onset AD to normal controls revealed that the odds ratios for strong psychological stress, depressed mood, and suicidal ideation were significantly increased in only adult-onset patients compared to those of normal controls (Yoo et al., 2022). This information suggests that practitioners should certainly take clinical phenotype and psychological health into consideration when caring for AD patients of varying ages.

Figure 2. *Progression of AD symptoms from infancy to adulthood with photos. Note: this progression does not represent all AD populations, but rather is meant to show how symptoms and disease severity can progress throughout a patient's life.*



I.3. Current Treatments and Side Effects

With debate in the literature regarding standardized diagnostic criteria among both child and adult populations, the discussion of AD treatment options is often a heated one. With little conversation about patient education and prevention in the form of lifestyle, most research and practitioners alike fail to equip individuals with the tools they need to heal in a more holistic manner. While there are many treatment options available, they all come with their own risks and complications, especially in the context of long-term usage. Regardless of age, a successful approach to AD management often involves a combination of interventions and avoidance of individual triggers– yet another element speaking to the complexity of the disorder (Katsarou & Armenaka, 2010).

The most popular types of AD treatments include topical agents. This includes both non-pharmacological interventions such as moisturizers and emollients, as well as pharmacological interventions such as topical corticosteroids (TCS), calcineurin inhibitors, antimicrobials and antiseptics, and antihistamines (Eichenfield et al., 2014). Topical steroids have served as the cornerstone of treatment since their introduction nearly 60 years ago but are most effectively used for brief periods (1 – 2 weeks) for quick control of moderate to severe disease flares (Simpson, 2010). However, cutaneous side effects can include purpura (when small blood vessels leak blood under the skin), acne or rosacea-like eruptions, and of greatest concern– skin atrophy, which increases with higher potency steroids, use on thinner skin, and older patient age. In addition, research has confirmed that systemic absorption does indeed occur with TCS use in AD, potentially suppressing the hypothalamic-pituitary-adrenal axis in long-term or high potency using patients (Callen et al., 2007; Patel et al., 1995; Simpson, 2010). While most literature admits to the fact that long-term monitoring of patient using TCS is lacking, most studies continue to suggest and encourage usage. The current review attributes this to the fact that most studies discussing steroid use happen to have a lengthy conflict-of-interest section listing one or more pharmaceutical companies, compromising the integrity of the pro-TCS recommendations.

This current review would do its readers a disservice in not mentioning the concept of topical steroid addiction and withdrawal (TSA/ TSW)– a highly debated and controversial topic among the dermatological community and patient populations around the world. The phenomenon has gained media attention with websites such as the “International Topical Steroid Awareness Network” (ITSAN), which is a nonprofit charity formed to raise awareness about the condition and provide support for patients, as well as patients themselves coming forward to discuss their own experiences after discontinuing usage of TCS (*About*

ITSAN – ITSAN, n.d.). Also referred to as "red skin syndrome," the condition involves erythema, intense itchiness, dry skin, burning, and secondary lesions. Symptoms are described after cessation of TCS or when increased use or dosage of TCS is required to prevent symptoms from recurring, suggesting dependency (Hajar et al., 2015; Hwang & Lio, 2022; Marshall et al., 2023). Due to the fact that TSA/ TSW has a wide variation of presentation and often manifests similarly to severe AD itself, the medical community has been known to question its existence (Marshall et al., 2023). If not to deny the claims entirely, some practitioners and researchers blame the existence of the condition on patients' improper use of TCS (Hwang & Lio, 2022). While misuse is certainly a part of the issue, this review believes that there is more to the story– if so many patients are making "the same mistake" with their TCS use, resulting in TSA/ TSW, then it is inefficient to merely blame the patients. There is a reason they are overusing the product– likely because they realize their AD returns quite quickly after discontinuation and they hope to seek relief. While pharmaceutical intervention is certainly necessary in some cases, the existence of a significant population of patients with a secondary condition arising from misuse sheds light on a major issue in the typical treatment of AD and awareness among the dermatological community. This review acknowledges the benefits of medical intervention when it is appropriate but will instead focus on a more holistic approach to treating and managing AD, in hopes of giving patients some alternative, life-style based suggestions they can incorporate into their treatment plan.

I.4. Extrinsic Factors

As already established, AD is a complex inflammatory disorder with involvement of many genetic, immunological, and environmental factors that are highly interconnected. Immune system dysfunction, a compromised skin barrier, and irregular patterns of genes such as filaggrin all play a significant role. However, many studies have also found links between extrinsic and environmental factors which contribute to AD and its severity– such as food and certain nutritional components, supplementation of certain vitamins and minerals, lifestyle practices such as stress reduction, and exposure to pollution and toxins (Hülpüsch et al., 2021). This is valid for both child and adult AD populations given that research has found the condition can clinically worsen by environmental or emotional factors (Silverberg et al., 2018). In regard to diet, which is the most hotly debated topic among the AD community, many studies state that the consideration of diet in this case only leads to severe and problematic food elimination (Hon et al., 2018). However, this review does not seek to

endorse unnecessary restriction, but rather to provide insights into foods that may positively or negatively impact AD flares. Overall, this review aims to explore lifestyle interventions for managing AD without reliance on pharmaceuticals, embracing a more holistic approach, with the hopes of equipping patients with AD with tools they can utilize to better manage their condition and improve their quality of life.

I.5. Inclusion Criteria

The present review is classified as integrative. Studies employing various research designs with no restrictions were considered. Both quantitative and qualitative studies were included in this review. Only articles in English were included but were not restricted based on country of publication. Inclusion criteria encompassed studies conducted on human subjects of any age, gender, or geographical location. Due to the lack of standardized vocabulary used to describe the condition, this review selected to include only literature which utilized the terms "atopic dermatitis" and "eczema." A recent systematic review of various research databases found that about 64% of studies used the term atopic dermatitis (AD), and about 47% used the term eczema, making this the most widely used nomenclature to describe the condition (Kantor et al., 2016).

Chapter II: Food and Diet in the Management of AD

II.1. Food Allergies, Intolerances, and AD

The role of diet has been historically implicated in the pathogenesis of AD, due to the interplay of food allergies (FA) and AD in atopic march and the atopic triad (Rustad et al., 2021; Sidbury et al., 2014). FA is defined as an immune reaction to proteins in the food that occurs reproducibly on exposure to a given food and is absent during avoidance; it can be IgE- mediated, non-IgE-mediated, or a mixture of both (Lopez, Yarrapu, & Mendez, 2024; Turnbull, Adams, & Gorard, 2014). IgE-mediated food allergies are characterized by the rapid onset of symptoms following ingestion, such as anaphylaxis, whereas non-IgE-mediated food allergies are characterized by subacute or chronic symptoms, such as those affecting the gut, lungs, and most notably– the skin, which can include AD or AD-like manifestation (Zhang et al., 2021). Studies have shown that FAs are quite common in patients with AD, but more so in children than in adults; notably, approximately one-third of children with refractory, moderate-severe AD have IgE-mediated clinical reactivity to food proteins, suggesting the prevalence of food allergy in the AD population is much higher than in that of the general one (Eigenmann et al., 1998). Similar research conducted shortly after, also on

children with AD, found that milk, eggs, wheat, and soy were demonstrated to be the most involved allergic foods (Niggemann et al., 1999). However, in a more recent study conducted with patients of varying ages, FA prevalence was found among 50.7% in patients with AD, and among those, 94.9% had non-IgE-mediated food allergies, suggesting that in AD patients, the most common FA is non-IgE-mediated FA when compared to IgE-mediated FA and mixed FA (Kwon et al., 2013). A final important element in this discourse is the concept of food intolerances, which are defined as non-allergic food reactions that do not involve the immune system, but can, for example, involve an organic pathophysiological process such as an enzyme deficiency (Turnbull, Adams, & Gorard, 2014). Some early studies have suggested the involvement of histamine and reduced histamine degradation in food intolerance, especially in the case of AD, supported by significant increase in AD after consumption of foods rich in histamine such as fish, cheese, cured meat, pickled cabbage, wine, and beer (Maintz et al., 2006; Wantke et al., 1993). These results suggest that such non-allergic reactions (intolerances) have been shown to cause exacerbation of AD (Worm et al., 2008). It is important to point out that existing nomenclature represents a great issue, as some studies differentiate non-IgE-mediated food allergy and food intolerance, while others use them interchangeably– likely contributing to the lack of clear information regarding these topics. Also interestingly, the discussion of food intolerance and AD in recent literature seems to be lacking, focusing more on FA and the debate in relevance of IgE versus non-IgE-mediated reactions. Overall, there seems to still be considerable confusion regarding the role of FA, food intolerance, and whether they exacerbate AD directly, indirectly, or are rather co-existing conditions. Regardless of the causative mechanisms of these issues, it is clear that identifying FA and/or intolerances can help improve symptoms in patients with AD (Kwon et al., 2013). The current review will utilize the clear involvement of food and diet in AD, without delving too far into where exactly that involvement stems from.

With all of this, the discussion of food as a factor of AD remains a highly controversial one, with many studies detailing the problematic nature of unsupervised elimination diets. Much of the research that exists fails to evaluate *why* patients seek to take matters into their own hands via changing their dietary habits but seemingly tries to shame them by insinuating doing so without medical guidance does more harm than good. Interestingly, one study found that about half of patients with AD did in fact discuss with a health professional, but when doing so, felt it was extremely unhelpful, suggesting confusion regarding the topic for both patient and provider (Chan & Ridd, 2019; Rustad et al., 2021). This, coupled with the aforementioned risks of problematic side effects from prolonged use

of TCS, as well as increased attention to diet in both medicine and media, sheds light on why patients may seek such alternative measures in treating and managing their AD. The current review does not believe this to be problematic so long as there is clear scientific basis for adding or limiting certain foods, within reason and never to excess. Diet represents a unique set of components which can certainly affect atopy in conditions such as AD, through its being a source of allergens, providing substrates for components which interfere with atopy pathology, and modulating inflammatory and immune-related responses– the interplay of food and AD is extremely noteworthy and deserves attention and exploration (Schütte et al., 2022). Rather than promoting extreme elimination diets or restriction, the current paper will rather aim to shed light on foods and nutritional components which may be helpful to incorporate or minimize in order to mitigate and improve AD symptoms and flares.

II.2. Anti-Inflammatory Diet

In recent years, the concept of adopting an "anti-inflammatory" diet has garnered increasing attention as a promising approach to promoting overall health and managing various anti-inflammatory conditions (Moriki et al., 2023). In particular, such a diet has emerged as a key factor in various chronic and atopic diseases, saying that certain nutrients and food components have the ability to modulate the immune system and in turn, prevent or mitigate the development of atopic diseases (Wu et al., 2019). Specific food groups and dietary patterns such as high fruit and vegetable consumption have been shown to be protective against both asthma and allergic rhinitis (Lahoud et al., 2020). As previously established, it is well known that the atopic triad consists of asthma, allergic rhinitis, and AD, suggesting an important connection, and likely similarities between the three conditions. Further supported by the concept of atopic march, linking the development of one allergic disease to subsequent others– there is reason to believe that if an anti-inflammatory diet is protective for asthma and allergic rhinitis, it may also be protective for AD.

Recent research conducted with children revealed that a pro-inflammatory diet pattern might worsen the atopic outcome by reducing patients' mitigating capacity against harmful environmental exposures and triggers. The study categorized pro-inflammatory diet as one where children consumed fewer vegetables, fruits, and nuts, but more meat/sausages and more sweets and snacks. Interestingly, researchers found that children that developed AD within the first 10 years of life also consumed significantly less fruits and nuts (Schütte et al., 2022). Notably, another study also suggested increased fruit consumption is associated with a decrease in AD symptoms in children (Lahoud et al., 2020). These studies, as well as many

others, have mainly focused on childhood prevention and treatment of AD, highlighting the idea that age and age of onset are relevant in terms of diet-related efficacy. However, the discussion of adults is also important, as we have already noted in this paper, adult AD can represent a much more severe, chronic, and debilitating manifestation. Surprisingly, many published articles seem to have found that anti-inflammatory diet does not modify the risk for AD in adults; however, it is crucial to note that these studies have been conducted on subjects with adult-onset AD, as well as on subjects with only mild AD (Bridgman et al., 2019; Moriki et al., 2023). Adult AD is only a small subset of the population, whereas the majority of cases begin in childhood and continue into adulthood (Margolis et al., 2014). A possible explanation for this may be that both adult-onset AD and mild AD do not involve as much systemic inflammation as AD that is chronic and early-onset (Chen et al., 2022). This may explain why the effects of an anti-inflammatory diet are not as effective in this particular population of adults, however, there is still reason to believe that such a diet may be helpful for adults with severe AD or AD which has persisted since childhood.

Notably, one small study showed significant improvement of AD symptoms in adults with severe AD after a two-month vegetarian diet. Patients self-reported significantly decreased severity in their AD, and serological parameters measurements indicated a sharp reduction in eosinophils and overall systemic inflammation (Tanaka et al., 2001). Anti-inflammatory diet in adults has been well documented with prevention and treatment of asthma and asthma symptoms. With the established relationship between asthma and AD, there certainly exists a notable link to be explored in terms of the same diet and AD (Han et al., 2020). The conversation of diet and AD is a complex one with many nuances; however, it is important to consider that while a solution is certainly not one-size-fits-all, it may exist for certain groups or even for some individuals– making it worthwhile to assess. Finally, it is important to note that following an anti-inflammatory diet has a wide array of other health benefits and has been consistently associated with lower morbidity and mortality from cardiovascular disease, diabetes, and many cancers (Itsiopoulos, Mayr, & Thomas, 2022). The important point here is regardless of the connection between these conditions and AD, following an anti-inflammatory diet is more likely to help most individuals than it is to cause them harm, highlighting a crucial difference between this type of dietary modification and an extreme elimination diet. This facet supports the notion that patients with AD should feel validated if they decide to pursue changes in their eating habits in order to help their condition or symptoms rather than being automatically being told they will only cause further harm.

II.3. Mediterranean Diet

Arguably the most popular and well-known example of an anti-inflammatory diet is the Mediterranean diet (MedDiet). It is a nutritional model which has been and continues to be universally appreciated, valuing Mediterranean culture, food quality, the means by which we obtain our food, and their land of origin (Altomare et al., 2013). The term refers to a traditional diet which is characterized by high intake of fruit and green vegetables, bread and whole grain cereals, legumes, nuts, low-to-moderate consumption of dairy products and eggs, and limited amounts of meat and dairy. It is also low in saturated fatty acids but rich in antioxidants, carbohydrates, fiber, monounsaturated fatty acids, and n-3 polyunsaturated fatty acids (PUFAs), mainly from olive oil and fish (Trichopoulou & Lagiou, 1997). Some specific elements of the diet that have been found to have strong anti-inflammatory effects include nutrients such as n-3 PUFAs from fish, polyphenols from extra virgin olive oil, and antioxidant components including β-carotene, vitamins E and C, and flavonoids from fruit and vegetables (Calabriso et al., 2016; Tangney et al., 2011; van Herpen-Broekmans et al., 2004).

The healing and protective nature of the MedDiet possesses many benefits for those with cardiovascular disease, metabolic disease, and has also been suggested to slow cognitive decline (Tangney et al., 2011). Recent findings in the last decade have also continuously supported the idea that the MedDiet has a low Dietary Inflammatory Index, suggesting its strong anti-inflammatory potential, and with this, the diet has been shown to minimize systemic inflammation and modulate the immune system (Itsiopoulos, Mayr, & Thomas, 2022). Due to the known interplay of systemic inflammation and AD, there is reason to believe that some components of the MedDiet may be beneficial for those with the condition. One study conducted about dietary modifications in AD patients based on patient-reported outcomes found that participants had the best improvement in skin when adding in vegetables, organic foods, and fish oil— all of which are known components of the MedDiet (Nostrati et al., 2017). Further, other studies have found that children who consume more fruits and nuts may be more likely to not develop AD or to have a decrease in AD symptoms, further supporting the idea that certain elements of the MedDiet may be useful (Lahoud et al., 2020; Schütte et al., 2022). Perhaps it is true that such a diet is most helpful in childhood, however, more research needs to be done in the field using patient-reported outcomes in adults with AD. It can be argued that due to the complex, individual, and variable nature of AD, patient-reported outcome studies may be the most useful in assessing what actually helps different populations of patients.

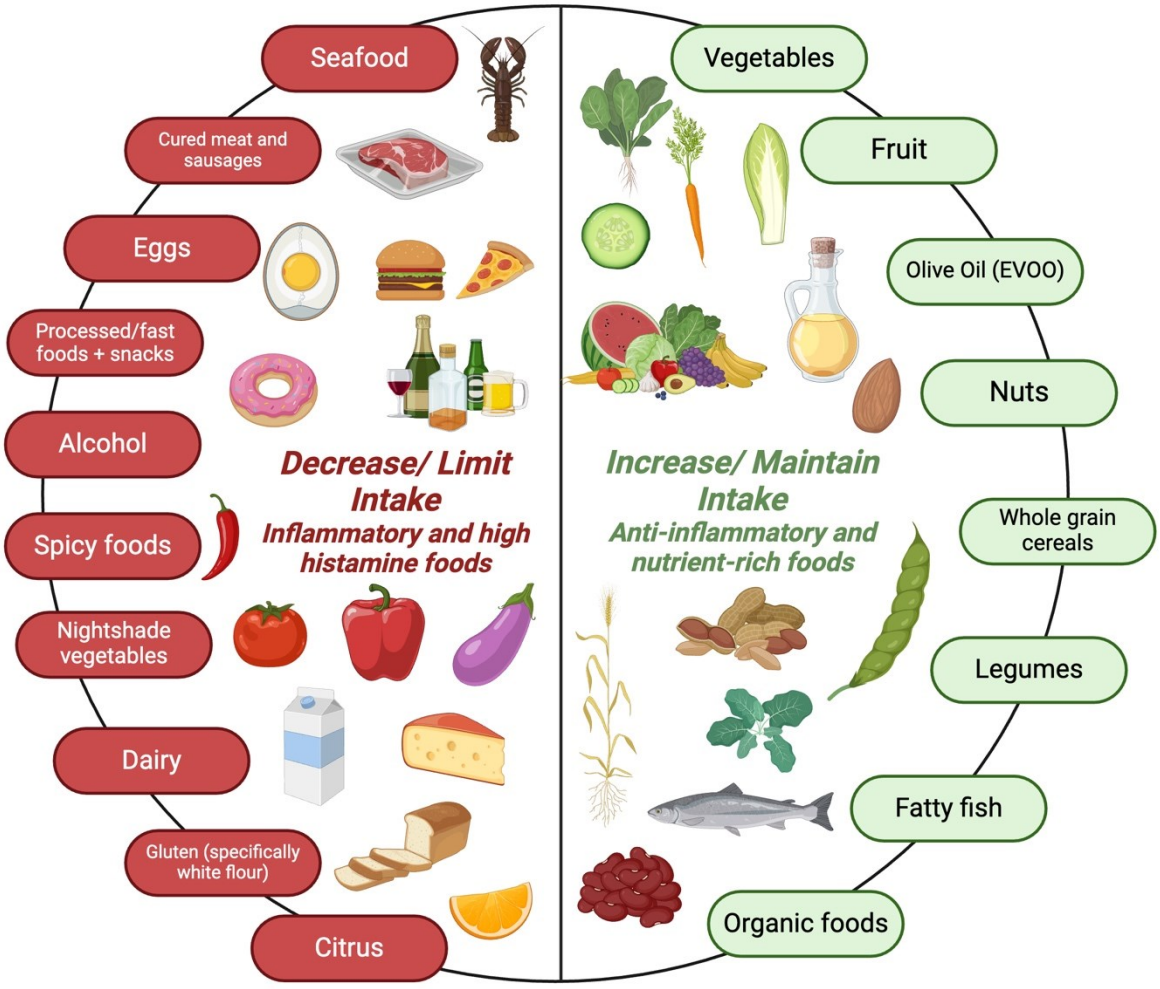
II.4. AD Dietary Triggers

In addition to the discussion of foods which can be potentially helpful in mitigating the effects of AD, an equally important facet is the avoidance or limitation of trigger foods. The concept of elimination diets is among the most controversial in the discussion of AD, with studies stating that blanket and strict elimination of foods without a clear food allergy have failed to lead to significant improvement in AD patients (Das & Panda, 2021; Neil et al., 2017). In some cases, excessive restriction of certain nutrients which come from allergenic foods can even lead to nutritional deficiency, potentially leading to worsened AD symptoms (Kim et al., 2013). Unsurprisingly though, if someone with AD is allergic to a particular food item, it can in fact trigger exacerbation of AD, and in these situations, avoidance of the allergenic food leads to improvement in AD symptoms (Das & Panda, 2021). However, this seems obvious, given the shared inflammatory nature of an allergic reaction and an AD flare, and essentially just supports the idea that whether or not AD is present, people should certainly avoid foods that they are allergic to. While eliminating many foods, or doing so randomly may not help AD, there is evidence that supports the idea that specific exclusion diets and dietary manipulation can play a role in AD management. Patient-reported studies have suggested that there are certain foods which may trigger AD symptoms and worsen flares. When asked what food or drinks made their AD worse, participants of one study stated that dairy (most prevalent), gluten, alcohol, sugar, tomatoes, citrus, and eggs (least prevalent), were the most commonly reported triggers. Less commonly reported triggers included meat, soda, spicy foods, processed foods, and seafood. Intriguingly, the best improvement of skin was reported when removing white flour products, gluten, and nightshades, which the study described as tomatoes, eggplant, peppers, paprika, and white potatoes. Also notably, 68% of patients reported a trial of avoiding/reducing junk food, and the majority of that percentage reported full clearance or improvement of their condition afterwards (Nosrati et al., 2017). This data was supported by a different study conducted in Korea, which found that consuming instant noodles, meat, and processed foods were associated with increased prevalence of AD (Park, Choi, & Bae, 2016). Of note, other research has found that children and adolescents that consumed fast food three or more times per week were at increased risk for severe eczema and AD (Ellwood et al., 2013). Food additives may be to blame for these associations, as they have been found to aggravate AD in adults (Worm et al., 2001).

While the effectiveness of blanket elimination diets for AD remains controversial, it is crucial to consider individual sensitives and allergic reactions to specific foods. Avoiding trigger foods, including but not limited to those which one is allergic to, can lead to

improvement in AD symptoms. However, indiscriminate elimination of multiple foods may not always yield significant benefits. Patient-reported studies suggest that certain foods, such as dairy, gluten, alcohol, and processed foods may exacerbate AD symptoms in some patients. Specific exclusion diets and dietary manipulation tailored to individual needs may play a role in AD management, with evidence indicating that avoiding certain food groups and additives can improve skin health in those affected with AD. Therefore, a personalized approach to dietary management, guided by patient-reported results, preferences, and clinical evidence is essential in optimizing AD treatment outcomes. All of this information regarding beneficial AD foods as well as potential triggers can be visualized in *Figure 3*.

Figure 3. *A visual guide categorizing foods for AD patients to limit due to their inflammatory or high-histamine nature and those to increase for their anti-inflammatory and nutrient-rich benefits.*



Chapter III: Nutritional Components & Nutraceuticals with Specific Benefits for AD

In addition to the established connection between diet and AD, it is also important to delve into how certain nutritional components (both those found in food and through supplementation) can play a role in the management of AD and its symptoms. It is known that nutritional status is necessary for a properly functioning immune system, and so it makes sense that it would be especially important for patients with AD, a condition with a clearly inflammatory nature and known immune system involvement (Vaughn et al., 2019). Whether it be that patients with AD are deficient in a particular nutrient, or that one can provide a particularly immune-protective effect, such components may be helpful in mitigating patients' AD flares, helping them to better control their condition.

III.1. Omega-3 and 6 Fatty Acids

In terms of having a potentially protective effect, omega-3 (n-3) polyunsaturated fatty acids (PUFAs), stand out in the case of inflammatory diseases. N-3 PUFAs are classified into three representative lipid groups: a-linoleic acid (ALA) (which is inefficiently converted to EPA and subsequently to DHA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) (Burdge, 2004). Due to the limited conversion of ALA, the beneficial effects of n-3 PUFAs arise mainly from DHA and EPA, which come from foods and/or marine dietary supplements containing fish oils (Sawada, Saito-Sasaki, & Nakamura, 2021; Simopoulos, 2002). N-3 PUFAs have been known to demonstrate anti-inflammatory actions in many inflammatory diseases, including asthma (Adams et al., 2019). Due to the known connection between asthma and AD within the context of atopic march, these findings could suggest a potentially similarly protective effect of n-3 PUFAs for AD. Further, EPA and its metabolites, such as resolvins, are known to demonstrate strong anti-inflammatory effects in allergic and inflammatory diseases (Sawada, Saito-Sasaki, & Nakamura, 2021). This has been thought to occur through EPA's reduction in pro-inflammatory cytokines (Crupi & Cuzzocrea, 2022). Notably, AD has both allergic and inflammatory involvement, with a known increase in IgE levels, sensitization of allergens, and predominance of Th2 cytokines (Yang et al., 2020). Sources of n-3 PUFAs include fatty fish such as salmon and tuna, fish oil, walnuts, and flaxseeds (Covington, 2004). Coincidentally, other studies previously mentioned in this review have found that fish, fish oil, and nuts had correlative effects on AD improvement in patients, supporting the idea that ingestion of n-3 PUFA-rich foods can be beneficial in management of AD (Lahoud et al., 2020; Nosrati et al., 2017; Schütte et al., 2022). Given these findings, it stands to reason that the intake of n-3 PUFAs, specifically

from fish-oil-rich sources, could prove highly beneficial in the management and alleviation of AD symptoms.

In terms of dietary intake, Western diets are deficient in n-3 PUFAs, and instead have excessive amounts of omega-6 (n-6) PUFAs. This is problematic because the two omegas are metabolically distinct; while n-3 PUFAs tend to have an overall anti-inflammatory and suppressive effect, n-6 PUFAs tend to be inflammatory and are believed to promote inflammatory and autoimmune diseases (Simopoulos, 2002). However, both n-3 and n-6 PUFAs are considered essential nutrients for humans, and the balance and source of the two seem to be the important factors in dictating their effect. The Western ratio currently leans heavily towards n-6 PUFAs that come from mainly processed fats and vegetable oils (cottonseed, safflower, soybean, canola), cereal-based products (white flour), and meat (Meyer et al., 2003; Simopoulos, 2002). The inflammatory nature of these particularly refined n-6 PUFA-rich foods can be especially problematic for patients with AD, as supported by a study which found that patients reported processed foods, meat, and white flour products to be triggers in worsening their AD symptoms (Nosrati et al., 2017). Nevertheless, it is intriguing to note that one meta-analysis found that Efamol® evening primrose oil (EPO) supplementation, a purely n-6 fatty acid, was found to have a beneficial effect on pruritus, crusting, edema, and erythema in AD patients after 4 – 8 weeks of treatment. The studies included in the analysis utilized daily doses ranging from 2 – 16 (500 mg) capsules per day depending on patient age, weight, and AD severity. While the study did not mention which dose was most efficacious, it was noted that the magnitude of any seen effect was reduced with increasing frequency of potent steroid use (Morse & Clough, 2006). Also interesting, another study found that daily dietary hempseed oil (30 mL), which is a rich and balanced source of both n-3 and n-6, caused improvement in both skin dryness and itchiness in patients with AD after 8 weeks of usage (Callaway et al., 2009). This possibly supports the idea that n-6 itself is not problematic, but rather its source, processing techniques, and level of intake. Overall, omega-related research conducted specifically in AD populations is lacking and there remains confusion regarding the exact role of n-6. However, there exists substantial evidence to support the notion that patients with AD may benefit from increasing their intake of n-3-PUFA-rich foods and/or supplements, while minimizing their intake of certain, highly manufactured n-6-PUFA-rich foods.

III.2. Polyphenols

Another group of micronutrients with a particularly anti-inflammatory effect is polyphenols. Different types of polyphenols are distributed among various types of plants and can be found in a range of dietary sources; flavanols (cocoa, tea, apples, broad beans), flavanones (citrus fruits), hydroxycinnamates (coffee, chicory, artichokes, plums, and pears), flavonols (quercetin in onions, apples, and tea), and anthocyanins (berries). Polyphenols have been shown to play a crucial role in suppressing inflammatory processes, with antioxidant, anti-microbial, and anti-allergic effects (Alverina & Sustanto, 2024; Williamson, 2017). Inflammation of the skin in AD is caused by infiltration of T-cells, pro-inflammatory cytokines, and eosinophils, leading to a debilitating itching sensation (Alverina & Sustanto, 2024; Talamonti et al., 2021). Research has found that dietary or topical polyphenols can reverse these inflammatory effects through inhibiting the activation, proliferation, and function of T-cell production and pro-inflammatory (Th2) cytokines (Singh, Holvoet, & Mercenier, 2011). Interestingly, one study found that patients with recalcitrant AD saw moderate improvement after 4 weeks of oolong tea consumption, which contains a type of catechin-derivative (a type of flavanol). Patients were instructed to make the tea (10 g teabag placed in 1000 mL of boiling water) and divide that into three equal servings. Beneficial effects were seen as early as one week but increased within the first month and were maintained at 6 months. These results were believed to be caused by the anti-inflammatory and anti-allergenic properties of polyphenols (Uehara, Sugiura, & Sakurai, 2001). Another study utilizing catechins, but instead those found in apples, was conducted in patients with AD. Patients receiving daily (10 mg/kg) apple condensed tannin (ACT) supplements for 8 weeks were found to report reduced inflammation, lichenification, and cracking scores compared to when they started the study. Notably, itching and sleep disturbance scores were lower compared to those of the control group, something which greatly affects quality of life in AD patients (Kojima et al., 2000).

Polyphenols, beyond their anti-inflammatory attributes, can further enhance skin health through their antioxidative properties. One study found that consuming high-dose oral cocoa-rich flavanols led to decreased water loss from the skin and increased dermal blood flow, which could be particularly helpful in AD-related skin dryness (Neukam et al., 2007). Another noteworthy aspect where polyphenols can offer benefits to patients with AD is in their ability to manage bacterial populations. As discussed earlier in this review, patients with AD are likely to have lesions colonized with Staphylococcal bacteria such as *S. aureus*, which is considered a secondary infection of AD and is known to worsen symptoms

(Hülpüsch et al., 2021). Research has suggested that polyphenols have the potential to help inhibit *S. aureus* virulence and enterotoxin activity (Choi et al., 2007; Singh, Holvoet, & Mercenier, 2011). While this could prove to be promising for patients with AD, more research using human subjects must be conducted in order to better assess which types of polyphenols may be most helpful for mitigating various AD symptoms. However, the research that has been done seems to suggest that increasing consumption of certain polyphenolic-rich foods, such as tea, cocoa, and apples, may serve to be a low-risk and holistic way of improving certain symptoms in AD patients.

III.3. Vitamins

III.3.1. Vitamin D

In addition to nutritional components and nutraceuticals that can have protective or anti-inflammatory effects on AD, it is also important to consider the role of vitamins and micronutrients. More specifically, it is important to understand how they influence the risk for AD, and how deficiency and supplementation may affect disease severity. Of all nutrients, vitamin D (vitD) is one of immense interest. Immunological studies have suggested associations between vitD deficiency and the development of AD and other allergic diseases, likely due to vitD's widespread modulatory effects on both the immune system and skin integrity (Mutgi & Koo, 2013). In accordance, one study found that serum 25-hydroxyvitamin D (25(OH)D) levels were lower among AD patients of all ages when compared to those of healthy controls– this was especially prominent in pediatric AD patients (Kim et al., 2016). Another study conducted only on adults found similar results, with serum 25(OH)D levels being significantly lower in participants diagnosed with AD than in those without the diagnosis (Cheng et al., 2014). Furthermore, low levels of vitD associated with deficiency have been shown to be inversely correlated with AD severity (Borzutzky & Camargo, 2013). Supporting this concept, in one study assessing vitD levels and AD severity in children, those with mild disease had significantly higher vitD levels compared to those with severe disease (Peroni et al., 2011). In alignment, a different study showed AD severity had inverse associations with serum 25(OH)D levels, and also that vitD deficient patients showed higher total IgE than those with insufficient and sufficient vitD levels (Wang et al., 2014). These results support the associations of high allergenicity and atopy with lower vitD levels.

In regard to the therapeutic role of vitD replacement in AD, supplementation has shown promising results in reducing disease severity and symptomology. Children who were

randomized to receive daily vitamin D_2 (1000 IU) for 4 weeks showed improvement and decreased AD severity when compared to the placebo group (Sidbury et al., 2008). Another study also involving children with AD showed similar improvements after receiving daily vitamin D_3 (1000 IU) for 4 weeks (Camargo et al., 2014). A final study evaluating a higher daily dose of vitamin D_3 (1600 IU) for 8 weeks found that receiving patients showed significant improvement regardless of their initial AD severity (Amestejani et al., 2012). Intriguingly, a study conducted on adults found similar improvements in AD symptoms from supplementation, but at even higher dosage and duration– daily vitamin D_3 (2000 IU) for 12 weeks (Samochocki et al., 2013). These results may suggest that adult patients with AD which has persisted throughout life may require a larger dose of vitD to see efficacious results. In addition to oral supplementation, some studies have evaluated the effects of heliotherapy (HT), a form of phototherapy using natural sunlight, as a method of vitD replacement therapy. In one study, adult AD patients received a two-week course of HT in the Canary Islands, increasing their time outside daily by 15-minute increments all the way to a maximum of two hours. Notably, before HT, 17 of 23 patients were vitD deficient, whereas after, only four patients remained deficient; further, this therapy caused a marked improvement in symptoms across all patients (Vähävihu et al., 2008). While these studies are limited in their sample sizes and short durations, they offer promising and low-risk results supporting the use of both oral and phototherapeutic vitD in the treatment of AD. More research conducted at a larger scale should be done in order to better establish guidelines for vitD supplementation dosage and duration.

III.3.2. Vitamin E

Vitamin E (vitE) serves as another micronutrient of interest in the case of AD. vitE, or tocopherol, includes a group of fat-soluble vitamins with strong antioxidant and anti-inflammatory properties (Vaughn et al., 2019). vitE is believed to have the ability to decrease serum levels of IgE in atopic patients, which could be linked with improvement of AD symptoms. In one study, patients with mild-to-moderate AD were given daily oral vitE (400 IU) for 4 months. Results indicated significant improvement in itching, lesion extent, overall symptom severity, and quality of life scores with no side effects. Notably, this improvement was sustained for 12 weeks after discontinuing supplementation (Jaffary et al., 2015). An earlier study also provided interesting insights– in the group of 50 AD patients receiving daily vitE of natural origin (400 IU) for 8 months, nearly half showed great improvement, and 7 showed almost complete remission of AD. In terms of IgE levels, subjects with great

improvement or almost complete remission demonstrated a 62% decrease in serum IgE levels when compared to baseline measurements. There was a remarkable improvement in facial erythema, lichenification, and decreased itching, which likely contributed to overall lesion healing (Tsoureli-Nikita et al., 2002). Another study evaluating supplementation of both vitD and vitE yielded noteworthy results: when taken together, subjects experienced greater reduction in AD symptoms than those who took vitD and vitE separately, suggesting a possibly synergistic effect of the two (Javanbakht et al., 2010). The significance of vitE in AD underscores its potential as a therapeutic avenue well worth exploring. Its antioxidant properties offer promise in mitigating oxidative stress and inflammation, both of which are implicated in AD pathogenesis. Further research elucidating the specific mechanisms of vitE's action and its optimal use in AD management is warranted, but current research certainly supports its use as an adjunctive therapy with no known side effects in the comprehensive treatment for AD.

III.4. Trace Minerals- Zinc

Next to vitamins, there are a variety of trace minerals which are essential for optimizing cellular processes throughout the body, and few studies have investigated the interplay of AD and various minerals such as zinc, selenium, and magnesium (Vaughn et al., 2019). Among all the minerals, the one which has been most closely explored for its possible benefits in AD is zinc. As a mineral, zinc possesses anti-inflammatory properties which have been shown to suppress inflammatory cytokine production, as well as antioxidative, and antibacterial properties— making it a pivotal tool in the dermatological world, especially for those with AD (Jones et al., 2008; Prasad, 2007). Also notable for AD, zinc is involved in the expression of filaggrin, an important skin barrier protein discussed earlier in this review, of which mutations are often found in AD patients (Maarouf, Vaughn, & Shi, 2018; Tsuji et al., 2018). Interestingly, one study measuring hair zinc levels in children and adolescents with AD found that those with the condition had significantly lower mean zinc levels compared to controls. After 8 weeks of daily supplementation (12 mg), however, hair zinc levels increased and eczema severity, pruritus, and sleep disturbance scores improved drastically compared to those who did not receive supplementation (Kim et al., 2014). In addition to playing a role as a micronutrient AD patients may be deficient in and need more of, zinc may also influence AD severity. A recent study found an inverse relationship between AD severity and erythrocyte zinc levels, which suggests that it may be useful in mitigating and minimizing symptoms associated with AD (Karabacak et al., 2016). Zinc may also be useful from a

topical perspective– one small study was conducted on AD patients who were given zinc-oxide (ZnO) textiles to wear for three subsequent nights; patient-reported results indicated pruritus severity decreased, as did erythema, edema, and papules. However, while the use of zinc in this way is innovative and certainly intriguing, this study was small and such textiles are often expensive, so they may not be feasible for most patients (Maaroug, Vaughn, & Shi, 2018; Wiegand et al., 2013). These results suggest a serious interplay between zinc and AD, but research conducted at a larger scale, both in sample size and duration must be done in order to better guide AD patients in the proper treatment using this vital micronutrient.

Overall, patients with AD should undergo blood tests in order to assess their vitamin, mineral, and micronutrient levels, and if deficiencies are identified, supplementation can be considered as a means to alleviate symptoms. This type of holistic treatment approach holds immense value for AD patients. Rather than merely addressing symptoms with topical treatments that target systemic inflammation, without addressing the underlying cause, patients and practitioners alike should aim to explore the root of the issue. In this case, serum testing may reveal a deficiency, which research indicates can in fact contribute to the exacerbation of symptoms and progression of AD. However, this same perspective can be applied in other facets of AD treatments, allowing for more comprehensive, effective, and tailored care– something which seems to be necessary for a condition as complex and multifaceted as AD. Information regarding all of the nutritional components which can be considered for AD management are summarized in *Table 1*.

Table 1. *Nutritional components with specific effects for AD patients.*

Component	Benefit/ Potential Harm	Dietary/ Supplemental Source	Study Source
Omega-3 polyunsaturated fat (n-3 PUFA)	- Anti-inflammatory effect in allergic and inflammatory diseases - Reduction in pro-inflammatory cytokines - AD improvement	Fatty fish (salmon, tuna) Fish oil Walnuts Flaxseeds Marine dietary supplements	2, 41-41, 114, 143, 167, 171, 186
Omega 6-polyunsaturated fat (n-6 PUFA)	- Can be inflammatory if n-6 to n-3 ratio is too high - Can be inflammatory if found in processed or ultra-processed n-6 PUFA-rich foods	Processed fats and vegetable oils White flour products Meat	133, 143, 186
Omega 6-polyunsaturated fat (n-6 PUFA)	- Reported improvement in pruritus, crusting, edema, & erythema	Efamol® evening primrose oil (EPO)	136
Omega 3 + Omega 6 PUFAs	- Improvement in skin dryness and itchiness	Dietary hempseed oil	24
Polyphenols	- Suppress inflammatory processes through inhibiting activation and function of T-cell production and pro-inflammatory cytokines - Antioxidant - Anti-allergic - Anti-microbial- can inhibit *S. aureus* virulence and enterotoxin activity	*Flavanols:* cocoa, tea, apples, broad beans *Flavanones:* citrus fruits *Hydroxycinnamates:* coffee, chicory, artichokes, plums, and pears *Flavonols:* quercetin in onions, apples, and tea *Anthocyanins:* berries	6, 188, 223
Polyphenols	- Moderate improvement in recalcitrant AD	Oolong tea *(flavanol)*	207
Polyphenols	- Reduced inflammation, lichenification, and skin cracking - Less itching and sleep disturbance	Apple condensed tannin (ACT) supplement	109
Polyphenols	- Antioxidative properties - Decreased water loss from skin - Increased dermal blood flow - Improvement in skin dryness	High dose- oral cocoa-rich flavanols	139
Vitamin D **AD patients are often deficient*	- Deficiency can be inversely correlated with AD severity and total IgE - Supplementation can reduce disease severity and symptoms despite severity - Modulatory effects on skin integrity and immune system	Daily oral vitamin D_2 or D_3 supplements (doses vary for children and adults) Natural sunlight	7, 20, 26, 101, 137, 178, 210, 217
Vitamin E	- Antioxidant and anti-inflammatory properties - Can decrease IgE serum levels - Improvement of AD symptoms	Daily oral vitamin E supplements Daily oral natural origin vitamin E supplements	86, 204, 212
Vitamin D + Vitamin E	- Greater AD symptom improvement in patients who took both together than separately - Possible synergistic effect	Daily oral vitamin D + daily vitamin E supplements	87
Zinc **AD patients are often deficient*	- Deficiency can be inversely correlated with AD severity - Suppress inflammatory cytokine production - Antioxidative and antibacterial properties - Involved in expression of filaggrin - Improved severity, pruritus, and sleep	Oral zinc supplementation Zinc oxide (XnO) textiles to wear	89, 95, 99, 126, 159, 205, 222

III.5. Probiotics

In the past few years, the power of human gut health and concept of improving it has garnered substantial attention throughout the healthcare and wellness sectors. The gut microbiome has been found to affect other organs, such as the skin, which has its own cutaneous microbiome. The two are highly related, and dysbiosis of one or both has been linked to alterations in immune responses and to the development and severity of skin conditions such as AD (Lee et al., 2018). Early in life, the gut microbiome is believed to shape the development of AD and other allergic diseases by regulating immune system maturation through crosstalk between the microbiome and the host. Alterations can certainly affect immune system balance via the production of metabolites, which in turn, can cause an inflamed microenvironment in the gut (Lee et al., 2018; Zeng, Inohara, & Nuñez, 2016). This inflammation contributes to dysbiosis and immune system imbalance, which can persist into adulthood and therefore contribute to AD disease course (Gensollen et al., 2016). At the center of modern research lie prebiotics and probiotics, which hold the potential to manipulate and improve gut flora (Gibson & Roberfroid, 1995, Rusu et al., 2019). Probiotics, categorized as live microbial dietary supplements that improve the balance of host intestinal microbiota, have been employed to alter the composition of colonic microorganisms (Gibson & Roberfroid, 1995; Hill et al., 2014). In holding the potential to alter the key components of the gut microbiome, which can in turn affect skin health, probiotics may offer a promising way to regulate dysbiosis in AD patients via their immunomodulatory effects.

The role of the intestinal microbiome may be where the role of probiotics may have the most substantial effect for AD patients. Probiotics can modulate the general microbiome and immune status of the host via improving the intestinal barrier– these effects may be responsible for reducing allergic responses and AD severity (Rusu et al., 2019). Research has shown promising results for the application of probiotics to the therapeutic management of allergic diseases, such as allergic rhinitis, with probiotic intake being associated with a significant overall improvement in quality of life scores and symptoms (Peng et al., 2015). Being that AD can also be considered an allergic disease, there is reason to believe that the immunomodulatory effects of probiotics may be helpful in such populations. Currently, the effects of probiotics in the prevention and treatment of AD remain quite elusive, however, research from different groups of patients suggest that depending on the specific probiotic strain, time of administration, and dosage measured in colony forming units (CFU), probiotics could have a positive effect on AD treatment (Rather et al., 2016). One small study utilizing the probiotic *Bifidobacterium breve* (~20 billion CFU/day) for 8 weeks in AD

patients showed significant decrease in disease severity scores when compared to those of the placebo group (Yoshida et al., 2010). A different probiotic strain, *Lactobacillus salivarius* LS01, was used in another study for 4 months (1 billion CFU/day), where results also indicated improvement in adult AD patients via self-reported parameters, quality of life improvement, and altered cytokine production– suggesting a reduced inflammatory response (Drago et al., 2011). Later, a different study suggested efficacy with a combination of the two aforementioned probiotics– *Lactobacillus salivarius* LS0 and *Bifidobacterium breve* BR03 in the treatment of adult AD patients. The patients who received a mix of the two probiotics (1 billion CFU/ each) twice per day for 12 weeks showed significant improvement as per clinical parameters, quality of life scores, and immunological parameters such as reduced immune activation (Iemoli et al., 2012). In a later study, oral administration of the probiotic *Bifidobacterium animalis* subsp *lactis* LKM512 (6 billion CFU/day) was found to alleviate itch in adult AD patients and improve quality of life scores compared to those of the control group (Matsumoto et al., 2014). While these results have been extremely promising, the sample sizes of the studies are quite small. Studies using a larger number of subjects with AD should be conducted to improve the generalization of these results and better understand which probiotic strains and dosages would be most beneficial in AD populations.

In addition to the intestinal microbiome, the cutaneous one is also significant in the context of AD. Skin, the largest organ of the body and our largest interface with the environment, is a complex ecosystem colonized with many microorganisms that, ideally, coexist in an established balance. However, in AD, this balance is often interrupted due to a compromised epidermal barrier and decreased microbiome diversity. This, in turn, correlates with disease severity and increased colonization of pathogenic bacteria such as *S. aureus*, further disrupting the already compromised cutaneous microbiome of AD patients (Paller et al., 2019). Commonly isolated from the skin of AD patients during flares, proliferation of *S. aureus* is thought to be encouraged by reduced competition from other microbiota, dysbiosis, and favorable growth conditions such as higher pH (Geoghegan, Irvine, & Foster, 2018). Further, membrane vesicles released from *S. aureus* bacteria can penetrate the epidermis and induce a substantial infiltration of inflammatory cells with a Th2 response, leading to more flares of AD (Jun et al., 2017). Interestingly, research has shown that consumption of the probiotic *Bacillus* bacteria has the ability to virtually abolish colonization of *S. aureus* pathogenic bacteria via a process of inter-bacterial competition between beneficial and pathogenic strains. The same study found negative correlations between *Bacillus* colonization of the human intestine with that of *S. aureus*, illustrating that the introduction of a beneficial

strain functions to remedy dysbiosis and eliminate presence of harmful strains which cause disease (Piewngam et al., 2018). This information can be summarized in *Table 2*. This perfectly illustrates how probiotics can be utilized in conditions such as AD, where patients have decreased microbiome diversity and dysbiosis.

Table 2. *Different probiotic strain(s) and their effects on AD patients.*

Probiotic Strain(s)	**Dosage**	**Benefits**	**Study Source**
Bifidobacterium breve	~20 billion CFU/day for 8 weeks	Patients showed significant decreases in disease severity scores when compared to those of the placebo group	236
Lactobacillus salivarius LS01	1 billion CFU/day for 4 months	Improvement in adult AD patients via self-reported parameters, quality of life improvement, and altered cytokine production	47
Lactobacillus salivarius LS0 and *Bifidobacterium breve* BR03	1 billion CFU/ each, twice per day for 12 weeks	Showed significant improvement as per clinical parameters, quality of life scores, and immunological parameters such as reduced immune activation	81
Bifidobacterium animalis subsp *lactis* LKM512	6 billion CFU/day	Alleviated itch in adult AD patients and improved quality of life scores compared to control	131
Bacillus bacteria	*N/A*	Ability to abolish colonization of *S. aureus* pathogenic bacteria	158

Chapter IV: External Environment & AD

The relationship between AD and the physical environment is a complex and multifaceted one. While up until now the effects of dietary manipulation, supplementation, and avoiding food triggers have been the focus of this review, the influence of the external environment in which we exist cannot be overlooked. Various elements of the physical environment, including place of birth, exposure to certain toxins, residence, and climate have been implicated in the onset and exacerbation of AD symptoms. This interplay of environment and skin can best be understood via the concept of epidermal barrier dysfunction. The skin barrier has been known to be damaged among patients with AD, predisposing them to harmful effects from exogenous agents– ultimately increasing their risk of allergen penetration, subsequent inflammatory reaction, and worsened AD (Cork et al., 2006). While this skin barrier dysregulation already allows for more prominent penetration of allergens, pollutants, and microorganisms, it is also known that environmental pollutants and chemicals further weaken the skin barrier– putting AD patients in a position where they are much more vulnerable to the environment than their non-atopic counterparts. This is especially true in children since their skin barrier is more susceptible to environmental damage than in adults, suggesting that perhaps the external environment has more influence at a young age (Shin et al., 2023). In understanding how these environmental factors can interact with both the skin barrier and immune system, we are brought closer to more comprehensive management strategies for this chronic, inflammatory condition.

IV.1. Hygiene Hypothesis and Place of Birth

Interestingly, place of birth and residence have been found to be factors which influence the occurrence of AD. Of note, the prevalence of AD has dramatically increased over the past 50 years worldwide; however, this prevalence appears to be higher in wealthier, more developed countries when compared with those which are less industrialized (Deckers et al., 2012; Kantor & Silverberg, 2017; Odhiambo et al., 2009). One theory which may explain this is called the "hygiene hypothesis." Originally coined in 1989, it postulates that exposure to various pathogens and infections early in life can strengthen the non-developed immune system against future allergic diseases and inflammation. In the same light, lack of this exposure may explain a rise in allergic diseases, such as AD, asthma, and hay fever in the 20th century (Strachan, 2000). More recent research regarding the "hygiene hypothesis" revealed more specific information suggesting an inverse relationship between AD and endotoxin, early day care, farm animal, and dog exposure in early life– suggesting these may

have the protective effects posited by the original hypothesis (Flohr & Yeo, 2011). In terms of birthplace and residence, more exposure to dirt and certain pathogens which might occur more so in a developing country may actually be protective against AD and other allergic diseases. Such differences in hygienic exposures among countries may account for a regional variance in disease prevalence (Kantor & Silverberg, 2017). In line with this, one study found that children born outside the United States (U.S) had significantly lower odds of developing atopic disorders such asthma, AD, food allergies, and hay fever, compared to those born in the U.S. However, the same study found that children born outside the U.S but resided there for over 10 years had higher chances of then developing atopic and allergic disorders compared to those who only lived there briefly (Silverberg et al., 2013). This information suggests that the protective effects which may be gained by being born in a less industrialized country and having more pathogenic exposure at a young age may wear off– supporting the notion that place of residence throughout life might be as important as place of birth. This may be useful from the perspective of AD management; while people cannot choose where they are born, they may be able to choose where they reside, and perhaps do so based on exogenous elements which best support their AD symptoms and overall quality of life.

IV.2. Urban vs. Rural Residence

In addition to variance in AD prevalence among geographical regions, there are also notable differences between urban and rural living. Previous systematic reviews have certainly revealed some evidence of a higher risk in AD and eczema in urban areas compared with rural ones (Schram et al., 2010). Aligned with the aforementioned U.S study, another found that metropolitan living, specifically in East Coast states, was a significant factor in predicting a higher AD disease prevalence (Shaw et al., 2011). One study conducted in China found that AD prevalence decreased from the center to the rural areas of Shanghai in young children (Xu et al., 2012). A more recent review found supporting evidence, concluding that people living in urban areas were 56% more likely to develop AD than those living in rural areas, but this effect was only significant for children and not adults (Shin et al., 2023). As previously discussed, the first and often most popular explanation to these results is the "hygiene hypothesis," which in this case, comes into play because children who grow up in metropolitan areas or larger cities are less likely to be exposed to certain exogenous elements which are more present in farming or rural environments. Children living on a farm in rural regions of Austria, Germany, and Switzerland were at significantly reduced risk for asthma and atopic sensitization compared with non-farm children. In this particular study, the effect

was explained by specific exposures to cows, straw, farm milk, and specifically for AD, manure (Illi et al., 2012). A later study conducted in South Africa found that in a rural environment, exposure to livestock was a strong protective factor against AD and other allergic diseases, and interestingly, in urban environments, consumption of fermented milk products served as a protective factor (Levin et al., 2020).

Similarly to the protective factors which may contribute to a lower prevalence of AD in rural areas, there exist several risk factors which may contribute to the higher prevalence in urban areas. The first to note is pollution levels, which are known to typically be higher in urban areas compared to in rural ones. One likely explanation for this difference in pollution is high vehicle traffic, which contributes to higher levels of traffic-related air pollutants (TRAP). Various studies have assessed the effects of these pollutants on allergic sensitization and asthma incidence, finding some evidence to support an association between traffic density close to the home with current asthma in children (Hassoun, James, & Bernstein, 2019; Nicolai, et al., 2003). Due to the close interplay of atopic diseases such as asthma and AD, there is reason to believe that similar findings could also be true for AD patients. Interestingly, one study found significantly higher levels of eczema and other atopic disease prevalence in polluted areas vs. nonpolluted areas (Dotterud, Odland, & Falk, 2004). In delving further comparing not only polluted vs. nonpolluted areas, a later study assessed AD incidence among urban and semiurban areas, finding a significantly higher prevalence amongst schools in urban areas which were exposed to more pollution (Sriyaraj, Priest, & Shutes, 2008). In addition to general prevalence, longitudinal research has also suggested that existing AD symptoms can also be aggravated by exposure to a variety of air pollutants including benzene, formaldehyde, volatile organic compounds, and nitrogen dioxide (NO_2). This is believed to be a result of oxidative stress, caused by an imbalance between oxidants and antioxidants in the skin barrier initiated by external pollutants (Ahn, 2014). From all of this information, it is reasonable to infer that individuals may be more likely to both develop and/or have increased AD severity if they reside in urban areas with substantial pollution– however, more research needs to be done in order to better understand the nuances of this, which air pollutants may be worse than others, and the exact mechanism by which these patients are affected.

Also of note, there exists a difference between diets in urban and rural communities, which could serve as another protective or risk factor for AD occurrence. Research has suggested that while both rural and urban residents at least, in part, rely on retail grocery stores, rural residents also rely on gardening and hunting, which may contribute to added

nutrients and fresher foods in rural diets (Smith & Miller, 2011). This makes sense, as rural communities tend to be in closer to proximity to farms, more land where animals can roam, and natural food sources than their urban counterparts. In line with this, one study assessing dietary habits among elders in both rural and urban regions of Korea found that intake of vegetables was significantly higher in rural elderly, and overall, they felt they had more "balanced" diets than urban elderly. Urban elderly on the other hand, were found to have higher intake of dairy products, meats, instant foods, snacks, and nutrient supplementation (Kim et al., 2012). As seen previously in this review, there is a clear association between diet and AD, with evidence supporting the notion a more vegetable-based diet may be protective, whereas a more processed one may pose risk for worsening symptoms. This information may suggest that diet and access to certain foods serve as a way to explain elevated prevalence of AD in urban environments. One study conducted in South Africa found that dimensions of an urban diet, which consisted of fried potatoes, carrots, tinned fruit salad, chicken, sausages, packet custard, and jelly, were strongly associated with positive skin tests, suggesting skin sensitivity and possible allergenicity. Overall, diet explained part of the difference in prevalence of atopic diseases between urban and rural areas, suggesting a valuable connection between the two which warrants being further explored (Hooper et al., 2008). Unfortunately, there exists a gap in the literature regarding urban vs. rural diet and its specific effects on AD, more research must be done in order to better establish evidence and give patients alternative tools to make more informed choices regarding their lifestyle modifications and ultimate management of their condition. However, what is currently known is that the prevalence of AD seems to be lower amongst rural communities, perhaps due to the "hygiene hypothesis," exposure to pollutants, diet, or a unique combination of the three. On the other hand, research suggests that AD may be worsened by these factors in an urban setting. While this review acknowledges that moving one's life, home, and family in a quest to manage their AD is likely not a viable option for many, this information remains valuable in that it may help patients in different parts of the world better explain and maybe even anticipate symptoms and flares. In having this knowledge, patients and physicians alike may elucidate this complex condition.

IV.3. Climate (Temperature, Humidity, UV)

In addition to geographical condition playing a potential role in AD, there also exists the influence of climate. Climate includes certain patterns of temperature, humidity, and ultraviolet (UV) light, which clearly contribute to human health. In addition to these

individual elements of climates, which have been suggested to influence AD, the presence of climate change over recent years is also noteworthy– serving as a potential explanation for disease prevalence over time (Nguyen, Anderson, & Davis, 2018).

IV.3.1. Temperature

The first important element is temperature. Interestingly, there seems to be an increased prevalence of AD during the winter months when compared to summer months, possible due to reduced sun exposure and thus, lower temperatures (Hancox et al., 2004). A later study conducted among Spanish school children also found a negative association between outdoor temperature and AD prevalence, suggesting higher temperatures promote decreased AD prevalence and vice versa. The same study also found that AD prevalence was lower in the Mediterranean region, but higher in the Atlantic region, which could also be accounted for by differences in temperature between those regions (Suarez-Varela et al., 2008). Likewise, in America, it was found that AD prevalence was lower in US states with a higher-quartile temperature. The reasons for this association are not exactly clear in the literature, but this study postulated that people living in warmer climates may use less indoor heating– which is another factor found to aggravate AD symptoms. Alternatively, people in warmer climates may spend more time outdoors, getting more UV exposure, which is also believed to be a protective factor against AD (Silverberg, Hanfin, & Simpson, 2013).

While this research certainly underlines a trend of higher temperatures correlating to lower AD prevalence, there have also been substantial studies showing contradictory results– that higher temperatures and increased sun exposure may actually be associated with poorly controlled AD (Sargen, Hoffstad, & Margolis, 2014). This contrasting information was especially highlighted in one study conducted among German schoolchildren. It found that 18 of 39 had worsened symptoms during summer months, however, 21 patients had worsened symptoms during winter months (Krämer et al., 2005). This may suggest individual types of AD and eczema play a role in determining temporal-based flares of the condition.
Also of note supporting more symptoms during the summer, one prospective study found that on the day of exposure, hot weather correlated to increased scratch scores in children with AD (Langan et al., 2006). This might be due to the fact that increased temperatures tend to result in increased perspiration or sweating, which can have an irritating effect on the skin, worsening pruritus, and overall AD symptoms (Langan, Silcocks, & Williams, 2009). In fact, multiple studies have described provoked sweating as one of the most commonly reported aggravates among children with AD (Kantor & Silverberg, 2016). It is possible that the

harmful role of sweat as an AD irritant comes from the acidic nature of sweat pH, which may promote Th2 inflammation– a known hallmark of AD (Sargen, Hoffstad, & Margolis, 2014). Another potential explanation for this may be the involvement of unmyelinated C-type nerve fibers which contribute to the origination of pruriceptive itch (McGlone & Reilly, 2010; Nguyen et al., 2018). These nerve fibers have been found to be more active at higher temperatures, which could explain increased pruritus in hotter climates or during warmer seasons (Pfab et al., 2010). Overall, the relationship between temperature and AD is a complex one which requires further study. For now, current research offers contradictory results, but it can be agreed upon that in patients with AD, there is a certain range of thermic and atmospheric conditions which create a perfect balance of both heat and water loss at the skin surface, which is most ideal for patients to be comfortable (Vocks et al., 2001). However, the valuation and specific understanding of this perfect condition is difficult to achieve and warrants further exploration.

IV.3.2. Humidity

After temperature, there is humidity, which is another considerable factor in assessing ideal environmental conditions in AD patients. Because the skin barrier is often derived of moisture in cases of AD, it is thought that patients fare worse in dry climates where there is low humidity (Nguyen, Anderson, & Davis, 2018). Even in healthy volunteers, exposure to dry environments where there is low relative humidity resulted in a decrease of skin hydration, making it appear clinically dry (Egawa et al., 2002). Interestingly, similar results were found in subjects who were transferred from normal and high humidity conditions to dry conditions. Further, those subjects had increased trans-epidermal water loss (TEWL) and reduced skin elasticity (Tsukahara et al., 2007). One study assessing factory workers and aircrew personnel, who are believed to be among the most heavily exposed to low humidity, were found to report significantly more skin-related symptoms such as itch, contact dermatitis, and AD compared to controls (Chou et al., 2007; Engebretsen et al., 2015). If all of this is true in volunteers without pre-existing AD, it is reasonable to believe that the same or even more extreme results would occur in an AD population with an already compromised skin barrier, predisposed to dryness and TEWL. One recent study found that patients had 1.6 times odds of presenting with AD during dry season compared to wet season in Nigeria, which was associated with lower humidity but higher temperatures (Ibekwe & Ukonu, 2019). However, it is important to reiterate that while humidity appears to help skin, and is popular among AD patients in the form of at-home humidifier, it can provoke sweating, which can be

aggravating and cause itch and discomfort. Similarly to temperature, the research regarding humidity is conflicting and requires further investigation.

IV.3.3. Ultraviolet (UV) Light

Also under the umbrella of climate is UV light, which serves as another potentially influential element of AD. Early research has suggested that UV radiation exerts immunosuppressive effects in both healthy and AD populations (Pearse, Gaskell, & Marks, 1987). Such effects on the human immune system via UV exposure promote production of regulatory T cells (Tregs), which act to suppress immune response; this could be useful in AD, where there a heightened immune response results in disease flares (Ullrich & Byrne, 2012). Another study found that low-dose exposure ultraviolet B (UVB) was found to strengthen the skin barrier and reduce morbidity in AD populations (Wulf & Bech-Thomsen, 2009). Along with these effects, UV radiation can also promote absorption of vital nutrients. Interestingly, humans obtain most of their vitD through exposure of skin to sunlight. UV's ability to induce vitD production is especially important in an AD population which is notoriously deficient in this key immune-regulating nutrient. In addition, this induction leads to down-regulation of cell-mediated immune function, also known to be a hallmark of AD (Hart, Gorman, & Finlay-Jones, 2011). Finally, another notable benefit of UV radiation is its suppressive effect in *S. aureus* production, previously discussed in this review as a commonality amongst AD patients often leading to a worsened condition. Intriguingly, children from Norway with severe AD were randomized to stay 4 weeks in Gran Canary, an island with a subtropical climate and high UV. Not only did bacterial skin colonization with *S. aureus* significantly decrease, symptom severity and quality of life scores improved, and use of topical steroids decreased when compared to the control group who remained in Norway. The results remained for 12 weeks after return, showing substantial evidence for the beneficial nature of climate where AD patients are exposed to more UV sunlight (Byremo, Rød, & Carlsen, 2006). Taken all together, it has been suggested that there exist two types of seasonal patterns in patients with AD– those who experience more flares in the summer during periods of high grass pollen exposure and high outdoor temperatures and UV, and those who experience worsened symptoms in the winter with low outdoor temperatures and decreased humidity (Krämer et al., 2005). This indicates a difference in mechanisms and further contributes to the idea that AD is a highly individual and personalized condition, reinforcing the notion that there will never be a one size fits all solution for everyone.

The relationship between AD and the physical external environment is intricate and significant. The impact of environmental elements such as birthplace, exposure to toxins, residence, and climate plays a crucial role in the onset and exacerbation of AD symptoms. The concept of the epidermal barrier dysfunction is central to understanding this interplay, as the compromised nature of the AD skin barrier leaves patients susceptible to allergens, pollutants, and microorganisms. This vulnerability particularly affects children, whose skin is more sensitive to environmental damage, however, elements such as residence and climate can certainly affect adult AD as well. Recognizing how these factors interact with AD and the immune system can lead to more effective and comprehensive management for this chronic inflammatory condition.

Chapter V: Lifestyle & AD

While genetic and environmental factors are well known contributors to the development and exacerbation of AD, general day-to-day lifestyle aspects such as sleep, stress, and emotions play a tremendous role. From a general perspective, it is certainly true that certain behaviors, routines, or management strategies may function as either harmful or helpful to our health, making our lifestyle choices an important component of overall well-being. This is especially relevant in the case of AD, which involves complex interplay between many factors, and is often misunderstood by patients and practitioners alike. In evaluating certain facets of lifestyle and their role in AD, patients can implore a more holistic healing approach, which will likely not only help them with their AD, but also with their general health.

V.1. Sleep

One of the first most vital components of health is proper sleep. Sleep is integral to overall well-being of all people, and with sleep disorders on the rise in recent years across the world, the topic is of utmost importance (Wells & Vaughn, 2012). Sleep health is defined as multiple sleep characteristics, including sleep duration, continuity, timing, alertness, and satisfaction; optimal sleep health has implications for many critical health outcomes (Hale, Troxel, & Buysse, 2020). Notably, poor sleep health is an important public health challenge, and is associated with morbidity and mortality (*Institute of Medicine (US) Committee on Sleep Medicine and Research*, 2006). While sleep is obviously vital for all individuals, it is of particular interest for AD patients. Disturbances in sleep quality from itching and soreness are some of the most commonly reported quality of life decrements in AD– reported in over 60% of patients (Lewis-Jones, 2006). It is believed that pruritus, a hallmark symptom of AD, often

worsens in a circadian manner at night, resulting in scratching that disrupts the process of going to sleep and staying asleep (Fishbein et al., 2015). This may be especially relevant in populations of children, who likely have less will to stop itching or take protective measures than adults may, leaving them more vulnerable to the effects of AD-related sleep disturbance. One longitudinal study found that in children, AD was significantly associated with impaired sleep quality throughout childhood (Ramirez et al., 2019). Similar results were found from another study utilizing actigraphy, a small wrist-worn device which measures estimated sleep-wake patterns using activity-based monitoring, and polysomnography, which found that subjects with AD aged 1-18 years had significantly reduced sleep efficiency, longer sleep onset latency (length of time it takes to transition from wakefulness to sleep), more sleep fragmentation, and less nonrapid eye movement sleep– all indicating extremely poor sleep quality. Interestingly, the same study found that low melatonin levels and high total serum IgE levels may play a role this sleep disturbance (Chang et al., 2014). Since high IgE is believed to play a role in AD manifestation and severity, it makes sense that sleep quality scores worsen with more severe cases of AD in children (Kong et al., 2016). Similarly in adults, sleep disturbances and sleep-related impairments were found to be common and especially in those with more severe disease (Li et al., 2018). This intense nocturnal pruritus has been found to drastically affect the quality of life in both children and adults. Specific to children, AD related-sleep disturbance is associated with behavioral problems, association with short stature, mood changes, impaired functioning at school, and also may affect their parents, causing impaired sleep for them as well, maternal depression, and parental anxiety (Chang & Chiang, 2018; Lewis-Jones, 2006). In adults, this sleep disturbance can cause increased number of sick days and doctor visits, poorer overall status, difficulty at work and with other instrumental activities of daily living, and negative effects on mental health and social functioning at work (Chang & Chiang, 2018). For both adults and children, it is certainly true that AD-related sleep disturbance can have tremendous effects on day-to-day life and overall well-being.

While patients with AD are clearly more likely to have sleep-related issues, it is also true that sleep is very necessary for AD healing and management. This negative loop of not being able to sleep because of AD symptoms ultimately leads to worsened AD, trapping patients in a viscous cycle. Parents of children with AD have reported that it is harder to prevent their children from scratching at night, and that they see that their child's AD often flares up more after a night of poor sleep, highlighting the fact that sleep disturbance itself may worsen the itch-scratch cycle so commonly seen in AD patients (Chang & Chiang,

2018). This could also be true due to the fact that sleep loss could lead to immune system dysregulation, which in turn could cause flares of AD or worsened symptoms (Besedovsky, Lange, & Born, 2012). In any case, there is reason to believe that improved sleep may lead to improved AD. One way in order to achieve this may be through melatonin supplementation. Melatonin is a hormone secreted from the pineal gland and is vital to sleep regulation; it has been shown to be effective in sedating those who struggle with insomnia or jet lag (Brzezinski, 1997; Chang et al., 2016). In addition, melatonin also has anti-inflammatory, immunomodulatory, and antioxidative effects, all of which have been shown to improve skin health and mitigate inflammation (Marseglia et al., 2014). Since nocturnal melatonin was found to be associated with sleep disturbance and greater AD severity in children, one study assessed the effects of giving children with AD daily oral melatonin (3 mg) at bedtime for 4 weeks. Interestingly, results revealed that after melatonin treatment, sleep-onset latency shortened and severity of AD improved when compared to the placebo group, further, no adverse events were reported, suggesting a small dosage of melatonin may be useful for children with AD in order to get them to sleep better and thus scratch less (Chang et al., 2016). However, despite some contradictory evidence, it is important to note that in the past, the National Sleep Foundation has warned against the use of melatonin in patients with immune system issues, as melatonin may have the ability to enhance certain immune functions (Kelsay, 2006; Touitou, 2001). More recent research has suggested that short-term use of exogenous melatonin is safe in some specific patient groups, but that long-term use may cause mild adverse effects (Anderson et al., 2016). Further investigation must be done in order to assess the safety of melatonin use in AD populations and also for long-term usage.

While the melatonin hypothesis at least makes sense both from an AD and sleep prospective with its duality of having both sedative and anti-inflammatory properties, the research remains extremely limited, especially in adult populations. Much of the other current literature suggests a more fragmented approach– treating the AD to improve sleep disturbance, or treating the sleep disturbance to improve AD, ignoring the intricacies of the connection between the two. In the first approach of treating AD to improve sleep, the suggestion is often systemic immunosuppressants, topical steroid therapies, or antihistamines, offering a blanket approach to merely mitigate the inflammation which influences AD, which is simply a short-term solution to a problem which will likely persist (Bawany et al., 2021). The second approach to treat sleep disturbance directly in order to improve AD, however, since there are no trials of medications used for insomnia conducted in exclusively AD populations, this approach actually has little to do with AD and more to do with treatment of

insomnia, or sleep disturbance itself. The idea behind this seems to be that if the patient can sleep well enough, they won't scratch. This approach often involves pharmacological substances such as various benzodiazepines which induce varying degrees of sedative effects. However, there are ongoing safety concerns with both short and long-term use of such substances which must be further evaluated (Bawany et al., 2021; Lavigne et al., 2019). Currently, there does not exist substantial research to suggest this is the way patients with AD should go about handling their AD-related sleep disturbance. One meta-analysis suggested that valerian root (*Valeriana officinalis L.*) may be a low-risk sleep aid for some, but studies have not been conducted specifically in AD populations (Shinjyo et al., 2020). Overall, while there is a strong evidence to support a cyclical relationship between worsening AD and sleep disturbance, there exists a significant gap in the literature in regards to the best way to deal with it. Perhaps the existence of this gap itself suggests that there is not a singular solution to this problem, and that true relief should rather be found through a more holistic approach to AD, one which connects ***all*** of the facets that could play a role in management of the condition.

V.2. Psychological Stress & Emotions

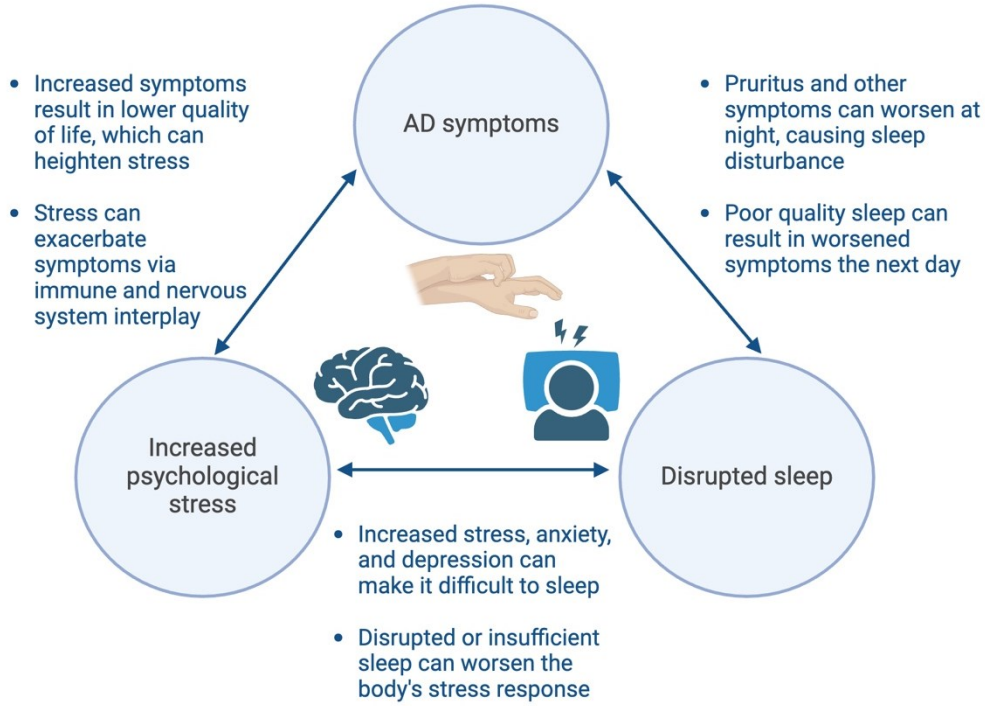
Not unrelated to sleep, another important lifestyle aspect which plays an important role in AD management is stress and emotions. Stress is defined as a general bodily response to initially threatening external or internal demands, which in turn involves physiological and psychological resources in order to cope. The rising field of psychoneuroimmunology, an interdisciplinary field focusing on the biochemical crosstalk between the brain, behavior, and the immune system, aims to explore the mutual activation and regulation of the nervous and immune system, assessing how one influences the other. It is believed that chronic stress, for example, has certain effects on different organ systems, especially the immune system, possibly resulting in a later Th2- mediated reaction, something which is known to be a hallmark of AD flares (Montoro et al., 2009; Suárez et al., 2012). It is true that both internal stressors, such as bacterial infections, and external stressors, such as psychological ones, may induce flares of AD via their impairment of the skin barrier function, which again results in a shift toward a Th2-mediated reaction (Arndt, Smith, & Tausk, 2008). Also in terms of skin barrier function, notable research was conducted on the relationship between psychological stress and epidermal barrier permeability barrier function in medical, dental, and pharmacy students without skin disease. Barrier function was measured at presumed periods of high stress, such as during final examinations, and also during periods of lower stress, such as

post-vacation, pre-examinations. After inflicted barrier disruption via cellophane tape stripping, subjects displayed improved permeability barrier recovery kinetics and lower perceived psychological stress during the period of lower stress compared to during the period of higher stress (Garg et al., 2001). Supporting the link between psychological status and cutaneous function in humans, it may be reasonable to assume that the same results would be even more prominent in an AD population, which has an already known damaged epidermal barrier function, possibly making them even more vulnerable to the effects of certain stressors.

Interestingly, one early study speculated that increased psychological stress in early childhood was associated with an atopic immune profile which includes a Th2 predominance which may persist throughout life (Wright et al., 2004). Under the umbrella of psychological stress exists the important topic of anxiety. Stress mediates anxiety, and is believed to worsen symptoms of AD and other skin diseases in predisposed patients. One study investigating this relationship found that AD patients had higher anxiety levels than normal controls, and also that high trait anxiety or baseline general anxiety was positively correlated with high serum IgE levels and Th2 shifting (Hashizume et al., 2005). In research investigating psychological distress, including anxiety, depression, and somatization in young male adults, results found that the odds of having each type of psychological distress were significantly greater for those with AD compared to healthy controls. Further, moderate-to-severe AD was related to depression and somatization to a greater extent compared to mild AD, suggesting disease severity might be relevant to the type of distress (Kim et al., 2015). Disturbingly, one study suggested that depression, anxiety, and suicidal ideation were more common among AD individuals, noting that moderate-severe AD patients also had increased likelihood to be taking antidepressant or anxiolytic medication than non-AD individuals (Thyssen et al., 2018). While these connections between AD and psychological distress certainly exist, their exact interplay is not entirely understood. It is interesting to consider the ordinal nature of the relationship between psychological stress and AD– is it that having AD contributes to higher emotional stress, perhaps due to a lack of sleep or lower quality of life due to persistent pain and scratching which is difficult to control, or is it that having psychological stress in the form of anxiety or depression worsens AD via the interplay between the nervous and immune systems, or is it is a cyclical relationship between the two (Solomon et al., 2018)? The complex nature of these elements can be visualized in *Figure 4*. Whether it is the chicken or the egg that came first, the two are clearly intertwined, and it can be reasonably assumed that patients with AD should do what they can to minimize their psychological stress. Of course,

this is easier said than done, as we live in a society full of reasons to be on-edge, however, certain stress-management techniques may be beneficial to manage these emotions, and are worth exploring, both as a method of improving AD and also general mental well-being.

Figure 4. *Cyclical relationship between AD symptoms, disrupted sleep, and increased psychological stress.*



V.3. Stress Reduction & Emotional Management for AD

While it is true that management of stress and emotions can serve to improve everyone's life, it may be of particular interest for AD patients. It is believed that stress increases serum IgE levels, and skews cytokine production towards Th2, which in turn enhances allergen-induced skin wheal (a raised, itchy area of skin) responses– all contributing to the AD cascade and symptoms (Kimata, 2003). Due to the viscous cycle of stress-related factors influencing AD flares, and AD flares creating substantial stress for patients, it is reasonable to believe that stress-reducing and emotional management strategies may be a vital part of overall, long-term control of the disease.

V.3.1. Psychological Interventions

In terms of therapeutic approaches, early case studies on adults with recalcitrant AD showed that insight-oriented psychotherapy resulted in skin clearing and overall psychiatric improvement (Sarti, 1998). Of note, one study found that after 6 months of brief dynamic psychotherapy, adults with AD with a higher level of anxiety were more likely to improve both their psychologic and dermatologic condition after therapy when compared to controls and those with lower levels of anxiety (Linnet & Jemec, 2001). A later meta-analysis found that psychological interventions such as psychotherapy and cognitive-behavioral therapy (CBT) had significant effects on ameliorating the effects of eczema severity, itching intensity, and scratching in AD patients. Interestingly, the same study found that CBT was especially useful in giving patients and parents of patients insight into AD-related problems, which could be utilized to restructure thinking patterns regarding the disease as well as other aspects of daily life (Arndt, Smith, & Tausk, 2008; Chida et al., 2007). CBT methods may resolve dysfunctional thought patterns which are cognitive, or actions which are behavioral, which can lead patients to damage their skin further or interfere with dermatologic therapy (Shenefelt, 2003). With this, patients can better control their own thoughts and actions surrounding their AD, gaining more control over their condition. More recent research conducted on adult AD participants found that internet-delivered CBT yielded substantial improvements in AD symptoms compared to the control group. Internet delivery of such resources could be extremely valuable as it provides access to many more patients without the use of extensive resources, providing an easy and beneficial adjunct treatment for patients (Lagerlöf et al., 2021).

V.3.2. Relaxation Interventions–Hypnosis, Massage, Meditation, & Mindfulness

In addition to a psychotherapeutic approach to mitigate stress and anxiety, there also exist other, perhaps more alternative interventions to induce a relaxed state. Some examples of this include hypnotherapy and hypnosis, massage therapy, mindfulness practices, and even meditation. Hypnotherapy involves guiding a patient into an altered state of consciousness and relaxation where they may be more receptive to suggestions. In terms of helping AD, such suggestions may include non-scratching behavior and that a person's skin will become "cool and comfortable," which may result in beneficial effects for the patient (Oska & Nakamura, 2022; Stewart & Thomas, 1995). An early hallmark study found that 18 adults and 20 children, all with extensive and severe AD which was resistant to conventional treatment were effectively treated using 2 – 7 weeks of hypnotherapy. Of note, improvements

itching and scratching, sleep disturbance, and in overall mood were reported to be maintained for up to 2 years in some participants (Stewart & Thomas, 1995). In another case study supporting the use of hypnosis, one adult patient with extensive and minimally responsive AD was subject to 15 sessions of hypnotherapy, after which they improved across all measured dimensions, which included itch, pain, insomnia, activity, anxiety, and emotional state both clinically and psychometrically. The authors of the study suggested hypnosis may be beneficial for its potential modulatory effects on immune and inflammatory processes (Perczel & Gál, 2016). A final recent study suggested similar results, where AD patients who had never had systemic treatment were offered a range of 2 – 16 sessions of hypnosis, and 26 of 27 showed significant improvement in their eczema severity scores after the sessions compared to baseline measurements taken before the sessions (Delaitre, Denis, & Maillard, 2020). Given the multifaceted nature of AD, it may also be true that it has a psychosomatic component, which may be the reason hypnosis is effective. It may also have to do with the mind-body connection which takes place when one is partaking in hypnosis, perhaps this heightened focus may promote some sort of healing. While the exact mechanism is not entirely understood, there certainly exists evidence to support the notion it may help those with AD manage their symptoms.

Another potentially useful relaxation intervention is massage therapy. Early research suggested that after 1 month of daily 20 minute massages done by their parents, young children with AD experienced improvements in affect, activity levels, anxiety levels, and also in redness, scaling, and pruritus when compared to the control group who only received standard topical care. In addition, the treatment also reduced parental anxiety, which is noteworthy, as parental anxiety surrounding AD is a well-documented symptom of the condition (Schachner et al., 1998). A few years later, another study showed significant improvements in eczema among two groups of children who received daily massages from their mothers for 8 weeks, either using aromatherapy essential oils or not. However, there were no differences between the improvements shown in the aromatherapy group and the control, suggesting there is no evidence to support the need for the oils. In fact, it may even be true that the oils could serve as an irritant or even a potential allergen source, so it is likely not worth the risk to use them in AD populations (Anderson, Lis-Balchin, & Kirk-Smith, 2000). Since then, there have not been many other studies using massage therapy in AD-specific populations, however, it is well known that massage therapy can certainly have substantial stress-reducing effects, thus, more research should be done in this population, in

order to assess its efficacy and also the best methodologies for employing it for those with sensitive skin and skin disorders.

Finally, under the umbrella of relaxation mechanisms is meditation and mindfulness practices. The two concepts are slightly different but related– mindfulness is the practice of bringing one's attention to the present moment, which involves being aware of thoughts, feelings, and bodily sensations. Whereas meditation is one method which can be used to achieve or cultivate mindfulness (Germer, 2004). Meditation can be done via many techniques, such as focusing the mind on a particular object, thought, or desired state. Both are famously known as stress-reducing techniques, which in turn are believed to be helpful with the management of conditions like AD, which can be triggered or worsened by stress. Both mindfulness and meditation practices have shown some evidence in improving chronic inflammatory skin conditions such as psoriasis and AD (Bartholomew et al., 2022). One early study conducted in patients with severe psoriasis assessed the efficacy of the Mindfulness-Based Stress reduction (MBSR) program, a stress management and prevention treatment developed over 30 years ago which includes mindful and conscious awareness of the body, bodywork, and meditation delivered by audiotape. All patients in the study were undergoing UV light therapy, however, those also partaking in MBSR had symptom resolution almost four times faster than those who had phototherapy alone (Kabat-Zinn et al., 1998). Due to the shared inflammatory nature of psoriasis and AD, there is reason to believe similar results could be replicated in an AD population. A later study assessing how mindfulness and self-compassion training might be useful in improving quality of life in AD patients found evidence to support this notion. In combining elements of MBSR and mindful self-compassion (MSC), which emphasizes building a compassionate relationship with oneself during times of suffering, another study was conducted in an AD-specific population (Neff & Germer, 2013). Participants who received 8, 90-minute group sessions of online mindfulness and self-compassion training for 13 weeks were found to have greater improvement in skin-disease specific quality of life attributes, as well as eczema severity, when compared to control groups who did not receive the training. This suggests that such training can be an effective adjunctive treatment for AD patients. Patients with AD often experience pain, discomfort, and other symptoms which are hard to manage, both physically and mentally. Due to this, they may also feel a sense of self-judgement, for example, for responding to an itch by scratching viscously, ultimately making it worse. Rather, the study posits that such programs can help teach patients that they have an option to respond more mindfully, such as apply a soothing touch; self-compassion on the other hand teaches there is no need for self-

judgement. While these skills are difficult to teach and cannot be adopted and utilized overnight, they serve as a potentially valuable tool for AD patients to shift their perspective surrounding their condition (Kishimoto et al., 2023). This information is extremely promising and offers patients a holistic way to learn to gain a sense of control around their skin. While more research must be done in AD-specific populations, there is certainly reason to believe that such relaxation methods have minimal adverse effects and substantial benefits if implemented into daily life.

V.3.3. Experiencing Joy— Movies, Music, & Human Interaction

As this review has already discussed, stress and negative emotions may aggravate AD, and AD itself also produces negative emotions, thus putting patients in a viscous cycle. Unsurprisingly, positive emotions are believed to have the opposite effect. Substantial previous research has reported that laughter itself has physiological effects and benefits (Schor, 2014). Interestingly, one paper which focused on patients with mild AD, assessed the effects of a humorous movie versus a non-humorous one. The results indicated that laughter associated with watching the humorous movie decreased measured serum IgE specific to allergens, while the non-humorous failed to do so (Kimata, 2004). Another study, by the same researcher, but additionally assessing the role of cell phones was conducted. The results indicated that while watching a comic video reduced all measures of allergic response, text messaging enhanced that response. Also of note, the comic video counteracted the mobile-phone mediated allergic response, but a non-comic video of the weather did not (Kimata, 2004). These findings seem to suggest that the stress induced from a mobile phone, just as one example, might make AD patients flare, whereas something which sparks joy and laughter, such as a funny movie, may be a good way to mediate that response. Music may serve as another sense of joy which can improve AD symptoms– one study involving adult inpatients with chronic pruritic skin disease, primarily eczema, were randomized to either a music group or an emollient group. The music group, which would listen to music following a U-sequence through headphones in a dark room for 20 minutes, showed significantly decreased pruritus compared to the emollient group, and also, 91% of the patients said that they would recommend the music intervention to others struggling with the same conditions (Demirtas et al., 2019). In terms of deep interpersonal connection, research has found that kissing can significantly reduce allergen-induced skin wheal responses in AD patients. Specifically, the study found that kissing down-regulated neurotrophin levels, which can subsequently down-regulate inflammatory cytokines, which are known to be a problematic

element of AD (Kimata, 2003). These results highlight the previously mentioned topic of neuroimmunology, suggesting that emotions can in fact have a substantial effect on the body and immune system. Future research should assess this topic more in an AD-specific population, especially in regard to types of human connections, sexual intercourse, and other activities that make humans experience joy.

V.3.4. Regular Exercise

Another popular form of stress management for all individuals is regular exercise. It is a potent tool which can help improve stress via the release of certain neurotransmitters that affect mood and behavior, such as dopamine and serotonin (Esch & Stefano, 2010). Exercise also stimulates the release of other endorphins and hormones which can have mood-boosting and pain-relieving effects, which can also help combat stress (Amir, Brown, & Amit, 1980). Further, studies have described an anxiolytic and anti-depressive effect of physical activity in healthy subjects and patients, suggesting it may be valuable in helping to control certain mental disorders (Ströhle, 2009). Thus far, a lot of research in exercise and stress has focused on aerobic exercise, a type which involves the slower, rhythmic, and repetitive movement of large muscle groups, such as jogging, yoga, swimming, or walking. There have been findings to support that people feel calmer after 20 – 30 minutes of aerobic exercise, and that this effect can last a few hours afterwards (Jackson, 2013). Since the connection of stress, mental well-being, and disease flares in AD patients has been well-established, it is reasonable to believe that regular exercise may be a helpful way for such patients to mitigate the stress which may in turn worsen their symptoms. However, while this logic makes sense, there are also certain physical components which may make it difficult for patients with AD to perform certain activities. Firstly, sweat is one of the most commonly reported exacerbants of AD in children, as it can cause increased itching and irritation of lesions (Williams, Burr, & Williams, 2004). In addition, the presence of these lesions themselves may be preventative, if they are for example located on the hands or feet. Finally, and most interestingly, the possible sleep disturbances, fatigue, and depression which AD patients experience could lead to lessened physical activity. One study specifically focused on this, finding that adult AD was associated with lower frequency of moderate-vigorous physical activity, and further concluded that this may have implications on cardiovascular health (Silverberg et al., 2016). Another later study conducted in adolescents found similar results, that those with AD had lower peak exercise capacity and lower weekly exercise volume than the control group without AD (Yang et al., 2022). While similar results have been found in a few studies, one

also found that despite the decreased desire to exercise in AD populations, those that did showed improvements in their mental health, suggesting that it can in fact be indirectly helpful to such populations (Kong, Koo, & Lim, 2020). In line with many other aspects of AD, it seems that patients can be caught in a viscous cycle, where their AD prevents them from doing the thing which may help them, ultimately worsening or failing to improve their condition. Regular exercise may certainly help ameliorate the negative stress and mental effects of AD, however, it may also irritate the condition if one sweats too much. Perhaps patients with AD should perform exercises which are low-impact, such as yoga, walking, or Pilates, which would allow them to get the stress-relieving benefits and develop healthy habits which accompany regular movement, without exacerbating their condition. Another option which has been previously mentioned is for them to workout indoors, or outdoors on cooler days. More studies should be conducted on human subjects in order to assess the best way for AD patients to incorporate movement into their lives, as well as to quantify the emotional benefits of exercise in this particular population.

While genetics and environmental factors are well-known contributors to the development of AD, there are also substantial aspects of lifestyle which are important and can play a role in management and improvement of the condition. Since there is no one-size-fits-all cure for AD, it is in the best interest of the patient to develop self-sustained habits and practices which can help them throughout their lives. This holistic perspective on AD is one which gives patients options, rather than simply suppressing their immune response using pharmaceuticals– this approach gives patients tools to better learn about their condition, how it is triggered, and how they can help themselves while also potentially improving other facets of their health.

Chapter VI: Complementary & Alternative AD Treatments

As previously mentioned in this review, patients may be frustrated with the lack of treatment options regarding their AD. In addition to making vital changes to their diet, lifestyle, and perhaps even the environment in which they spend time, some may also opt for alternative treatment options, such as herbal remedies and acupuncture. One early study described that about half of patients with AD reported previous or current use of one or more forms of alternative therapies. Interestingly, this usage was related to inefficacy of therapy prescribed by physicians (Jensen, 1990). Usage of such alternative therapies may certainly vary across the world, perhaps being less frequently utilized in places where Western medicine and pharmaceuticals are more prominent. Despite the controversy that seems to

follow alternative treatment options, AD patients should have choices other than suppressing their inflammation through immunomodulating drugs which often have other side effects. If done responsibly, in a way which is informed, alternative treatments for AD can be a valuable tool for patients who are struggling to control their disease flares. It is true that patients with this chronic condition are often forced to think outside the box in order to link together aspects which may help or harm them. This review believes it is beneficial to maintain an open mind when it comes to treatment options, and that the more one a patient is educated on, the more control they have over their flares and condition. Further, physicians should also educate themselves on such alternative measures, in order to best guide and support their patients.

VI.1. Herbal Remedies

Herbal remedies for skin disorders have been used throughout history for centuries. There are two well-known systems which are still in place– Ayurvedic herbs from India, and herb combinations as part of traditional Chinese medicine (TCM). While these are very accepted for their healing properties in the East, usage has historically been less prominent in Europe and the United States, where synthetic pharmaceutical drugs are more readily available and accepted. However, in recent years, with the increase in awareness regarding the potential negative effect of pharmaceuticals, the use of herbal remedies is beginning to resurge (Shenefelt, 2011).

VI.1.1 Ayurvedic Medicine

Ayurvedic medicine is based on the idea that the human body and universe are both made up of five energy elements– earth, water, fire, air, and space. The interactions of these elements then give rise to three *doshas*, or forces, and all diseases, including those of dermatological nature, are a result of an imbalance between these forces (Bedi & Shenefelt, 2002; Shenefelt, 2011). Similarly to the perspective by which this review is written, the pillars of Ayurvedic medicine suggest that managing any type of illness requires a look at all facets of one's life. Rather than the Western mentality of simply medicating to mask symptoms, this view proposes a holistic look at the imbalance in one's life as a means to discover the root of the condition. While more formal trials must be done in using specific elements of Ayurvedic medicine in AD populations, the mentality is an interesting and worthwhile one for patients and physicians to adopt.

VI.1.2. Traditional Chinese Medicine (TCM)

Similar to Ayurveda, TCM, also referred to as traditional Chinese herbal medicine (CHM), has been practiced for thousands of years. TCM focuses on treating the whole person and their lifestyle rather than just their symptoms. It is based on the complimentary forces of *yin* and *yang*, which are balanced in healthy people. However, an imbalance of the two is believed to result in illness. Each of the five recognized elements– earth, water, fire, air, and metal, are each related to specific organs, and are interconnected through the body's energy flow via 14 major meridians (Bedi & Shenefelt 2002; Shenefelt, 2011). Through a mixture of herbs, massage, and acupuncture, TCM treatment aims to restore necessary balance to the body, and in doing so, helps to heal individuals of their ailments (Latchman et al., 1994). One important element of TCM is the identification of disease patterns, which are determined by a collection of symptoms which are produced by specific causes and are meant to guide the practitioner to properly treat the condition. The patterns are usually named after pathogenic factors with metaphors from nature (heat, dry, damp, wind, and cold), meant to reflect the manifestation of the condition. This is especially important for a condition like AD, which has many different manifestations depending on a wide array of factors such as age, severity, and type, because it highlights the complexity of both the condition and its treatment. For example, if the AD is red and diffuse with dry scales, TCM may say that it is due to *"heat in the blood with wind,"* pointing to the redness as facet of heat, and dryness as one of wind. The herbal treatment for this might be one to cool the blood and scatter the wind. A more popular one is the *"damp heat"* pattern, which refers to AD which is red, swollen, and oozing fluid, where the herbal treatment might be to dry the dampness and cool the heat (*An Introduction to Chinese Medicine Dermatology*, n.d.). The use of TCM for AD is quite prominent, and continues to gain attention over time, especially as more and more patients are discovering the hidden dangers behind treatments like TCS. Due to the fact that TCM herb mixtures are typically individualized for every patient, depending on their specific manifestation of AD, standardized research is difficult to perform and thus isn't plentiful. However, a few studies have been conducted with promising results.

One systematic review concluded that TCM herbal medicine significantly improved AD severity including erythema, pruritus, and sleep quality when compared to the placebo. Interestingly, the same study found that combining TCM with Western medicine was superior to Western medicine alone, supporting the idea that patients should be open to utilize a variety of treatment modalities together (Tan et al., 2013). In terms of the specific herbal preparations, one study found that an 8-week course of oral *Xio-Feng-San* (XFS)

significantly ameliorated disease severity, itch, surface skin damage, and sleep loss compared to the placebo group who was not receiving the formulation. This herbal remedy includes a blend of 13 different medicinal plants with various qualities, including being anti-inflammatory, anti-bacterial, moistening, immune-modulating, and pain and itch relief (Cheng et al., 2011). Among 87,573 prescriptions written for Chinese medicine in a Taiwan hospital, XFS was the most frequently prescribed for AD patients (Lin et al., 2014). Interestingly, XFS was also recently explored as a treatment for chronic urticaria, which, similarly to AD, is characterized by redness and intense itching. The study found that quality of life in treatment groups improved, and serum inflammatory cytokines associated with the disease decreased, which may be part of the reason the herbs were also effective in AD populations (Yang et al., 2018). A different study assessed the efficacy of two different TCM compounds both together and separately in an AD population– *Hwang-Yeon-Hae-Dok-San* (TJ-15), a mix of four medicinal plants which has reportedly been effective in treating noninfectious chronic inflammatory conditions, and *Ou-Ryung-San* (TJ-17), a mix of five medicinal plants known for managing edema. This specific blend of compounds was hypothesized to be useful for the treatment of AD which follows a *"damp heat"* pattern, meaning inflamed, oozing, and red, and dosages were individualized depending on patient weight. In both the TJ-15 and TJ-15/TJ-17 groups, symptoms reduced significantly, suggesting this type of treatment based on pattern identification may be extremely valuable in an AD population with such a complex array of manifestations (Choi et al, 2012). A recent review reached a similar conclusion, finding that oral use of CHM formulation improved health-related quality of life in children with moderate-severe AD (Gu et al., 2017). Overall, it is certainly true that there is evidence to support the use of TCM/CHM both on its own and in tandem with Western medicine, however, this integration is difficult, and many Western practitioners are ignorant about Chinese medicine and may be opposed to it due to a lack of understanding, openness, and knowledge (Hon et al., 2017). It should be noted that while no dangerous adverse effects were found in any of the aforementioned studies, some TCM herbs and compounds may have pharmacotoxic effects such as drug interactions, variability in contents, and even potential contaminants. Further, another potential downside may be the taste, as some participants have stated they are unpalatable, particularly for children (Vieira et al., 2016). Despite this, the current yet limited research is extremely promising, as are the thousands of years of TCM history in treating AD. Researchers should continue to explore this topic in hopes of creating more specific treatment plans utilizing TCM for different patients. Even if patients or practitioners do not wish to use the herbs specifically, they

should utilize the valuable perspective of Chinese medicine; one which treats the entire individual and views the body as an interconnected system, rather than just a series of random symptoms which should be resolved without delving deeper.

VI.2. Acupuncture

Another ancient form of TCM is acupuncture. Acupuncture is the technique of insertion and manipulation of very thin needles in specific points in the body in order to achieve therapeutic purposes (Chon & Lee, 2013). Anatomically, acupuncture points are believed to connect to larger organ systems, and when stimulated properly, can have physiological effects on those systems (Andersson & Lunderberg, 1995). While originally and most typically used as a method of pain management for chronic and non-chronic pain conditions such as osteoarthritis, headaches, neck pain, and fibromyalgia, there is also reason to believe acupuncture may also work well for AD patients (Kelly & Willis, 2019). Research has previously suggested that acupuncture may have an anti-itch effect, specifically in allergic skin disease. One study showed that after exposure to an allergen stimulus, AD participants who received acupuncture at points *Quchi* and *Xuehai* had significantly lower mean itch intensity than controls (Pfab et al., 2010). Other studies conducted in AD populations using acupuncture have also suggested positive results. When one group of participants were given acupuncture three times weekly for 4 weeks, and another twice weekly for 4 weeks, both groups showed significant improvement among pruritus, insomnia, eczema severity, and dermatological quality of life measures; there were no clear differences between the two groups (Kang et al., 2018). While acupuncture can be used with or without herbal therapies, it may be more effective when used simultaneously. Adolescent and adult patients with mild-severe AD were given a combined treatment of twice weekly acupuncture and Chinese herbal formula three times per day for a total of 12 weeks. Fascinatingly, after completion of treatment, 100% of patients noted an improvement in their eczema severity when compared to their baseline scores, with no adverse effects reported (Salameh et al., 2008). Another similar study was conducted utilizing oral CHM three times per day and "Flying Needle" acupuncture three times per week, a specific method of acupuncture which has a unique curative effectiveness in improving skin lesions and itch. After 12 weeks of treatment, all patients showed improvement in their disease severity with no negative side effects (X Quan et al., 2014). While the small size of these studies may have contributed to the results, it is very rare and notable to see that a particular treatment helped every single patient who participated.

These positive anti-itch and anti-inflammatory effects may be due to the fact that acupuncture reduces activity of parts of the brain (insula, putamen, premotor and prefrontal cortical areas) induced by itching, which was demonstrated in one study using functional magnetic resonance imaging (fMRI). This may suggest that the anti-pruritic effects of acupuncture are mediated by the central nervous system and may also be due to the excretion of dynorphin, a neuropeptide involved in pain which can also have an anti-pruritic effect when acted on the insula and putamen. Activation of these mechanisms may be the reason that patients in the aforementioned studies have shown improvements in their AD with acupuncture (Napadow et al., 2014; Kang et al., 2018). Overall, while more research should be conducted on larger sample sizes, there is reason to believe that acupuncture may serve as a valuable tool for the AD community, for its pain, itch, and inflammatory relief properties, as well as its relaxation and anti-insomnia ones.

Likewise with TCM, patients and practitioners alike should be open-minded and willing to learn about these time-honored practices, as they have been around for thousands of years, helping people far before there were pharmaceuticals readily available. While this review does not oppose the use of Western medicine by any means, it is worth stating that there appear to be more risks, for example, with TCS than with an alternative treatment like acupuncture or herbal remedies. Further, there is a valuable lesson to be learned from these ancient, holistic methods of healing, where the individual is viewed as a whole, and all symptoms represent some sort of imbalance in the body which must be restored in order to achieve optimal health. This perspective also highlights the need for a multi-faceted approach, using diet, lifestyle, and alternative treatments, as this review proposes, to heal AD, rather than simply looking to mask the symptoms in the short-term.

Chapter VII: Conclusion

AD is a complex and chronic condition which involves interplay of genetic, immunological, and environmental factors. These factors contribute to the two main components of AD pathogenesis, which is immune system dysfunction and skin barrier abnormalities (Yang et al., 2020). In addition to the symptoms themselves, which include intense itching, dryness, redness, and lesions, the condition also has many effects on patients' mental well-being and overall quality of life. Manifestations of the disease often differ among and between both child and adult populations, making diagnosis and treatment planning difficult. The topic of current treatments is often a hotly debated one, with pharmaceutical interventions such as TCS and calcineurin inhibitors being widely used by physicians, often

without sufficient acknowledgement of the harm they may cause if used improperly and/or for too long (Eichenfield et al., 2014; Simpson, 2010). Unfortunately, despite whatever information is available regarding TCS, misuse is quite common, and can result in a secondary condition called TSA/ TSW, or "red skin syndrome," which involves symptoms similar to those of AD, but more intense, temperamental, and uncontrollable (Marshall et al., 2023). The condition begins after cessation of TCS use, suggesting dependency. While some practitioners and literature dismiss the concept of TSA/ TSW altogether, others attribute it fully to patient misuse of TCS (Hwang & Lio, 2022). However, if so, many patients continue to fall victim to misuse, there is a much larger issue at hand. From a young age, patients are given what they believe to be a miracle treatment- one that suppresses the irregular immune response which causes their AD flares, and of course, reduces their symptoms quite quickly and effectively. However, this treatment is only a temporary solution to an often-lifelong problem. Patients are rarely educated on ways which they can manage their symptoms in a more holistic way and are thus left to rely on pharmaceuticals which can have damaging long-term effects. Perhaps this is in part due to the strong economic impact that pharmaceutical companies have in many parts of the world, where increased disease incidence often translates to monetary gain. Whatever the reason, as time goes on, more and more patients have and will become curious on ways to manage their condition in a more natural way, and this review serves to provide information to patients who are seeking ways to do so.

This review believes that if patients are educated on ways to modify their lives, may it be through diet, environment, or behavior, there would be less incidence of TSA/ TSW. Perhaps patients would still use pharmaceuticals in short bursts, but they could have more autonomy and options for their care, therefore allowing them to not become dependent on one treatment. AD, being the complex condition it is, without a specific cure, should be managed through a comprehensive analysis at one's life. With a better understanding of different elements which may contribute to periods of either disease flare or improvement, patients can aim to live their lives in a way which best helps their condition. In the case of AD, these elements may relate to diet, intake of specific nutrients, the external environment, or lifestyle factors such as sleep and stress. In making changes and living one's life accordingly, patients can effectively manage their flares and improve their overall quality of life without negative side effects. In fact, it is often the case that such modifications actually benefit one's overall health in addition to improving their AD.

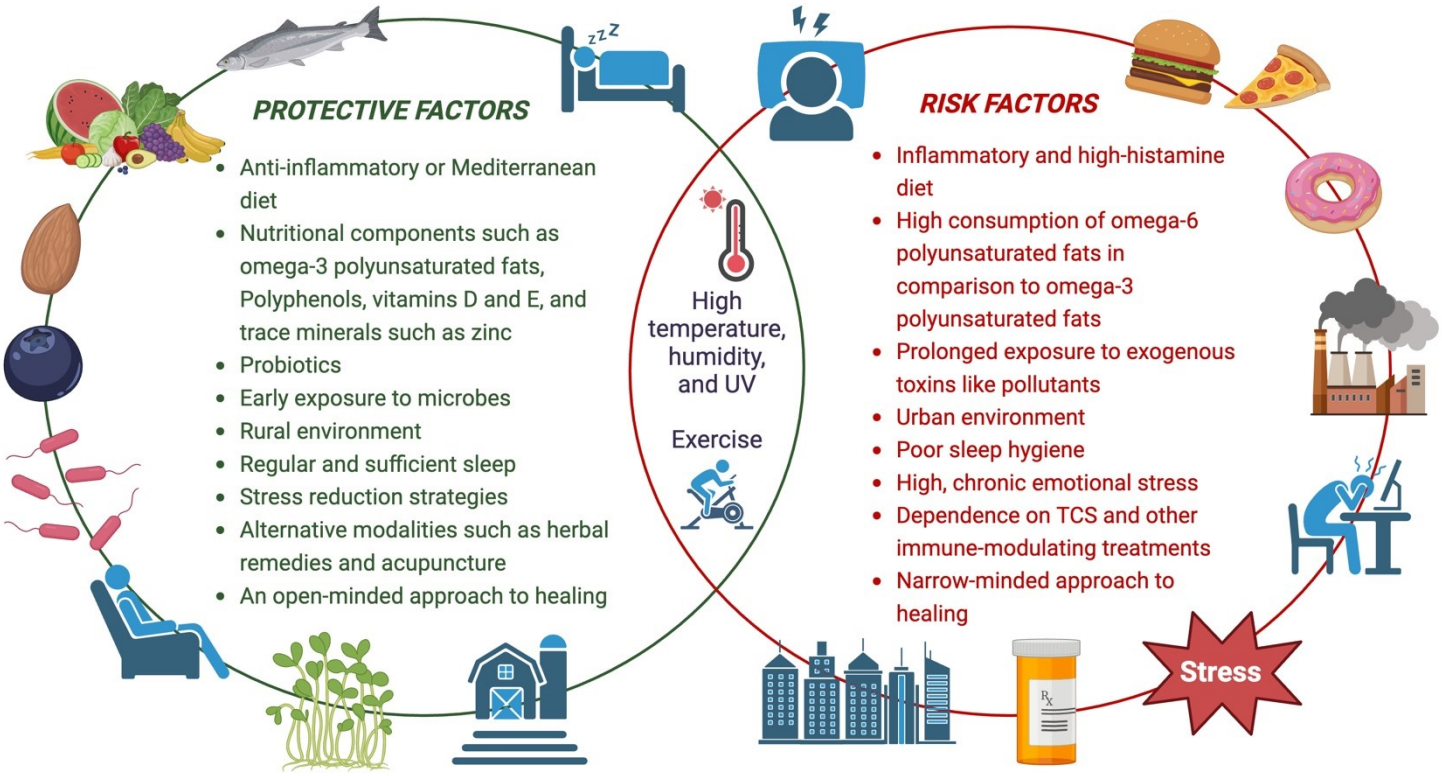
Diet and intake of various nutritional components may be the most important ways patients with AD can manage their condition. Interestingly, the topic of diet and AD is often scrutinized, with a lot of literature pointing to the restrictive and problematic nature of elimination diets. However, this review does not suggest that patients cut out many foods, but rather, looks to inspire readers to be more mindful about which foods may affect their AD in a negative way, and which may actually help mitigate symptoms. In establishing this connection, people can make more informed choices about their diets. While the goal is not to promote elimination or any fear surrounding food, there are certainly some foods that have been suggested to worsen AD symptoms, such as certain dairy products, gluten (mainly white flour products), alcohol, refined sugar, processed foods, citrus, meat, and eggs (Nosrati et al., 2017). Patients may want to at least lessen their intake of these foods gradually, in order to see if their symptoms improve. On the other hand, patients can also aim to eat an overall more anti-inflammatory diet, such as the MedDiet, which is high in fruits, green vegetables, legumes, nuts, and healthy fats from olive oil and fish (Trichopoulou & Lagiou, 1997). These foods have properties that can reduce systemic inflammation, a key component that fuels AD. In addition to dietary intake, there are also various nutritional components and nutraceuticals which have specific benefits for AD. Patients with AD are often deficient in certain vitamins and minerals, and restoring balance of those within the body may correlate to symptom improvement or resolution; therefore, they should undergo blood tests in order to assess their levels. Foods or oral supplements rich in n-3 PUFAs, polyphenols, vitamins D and E, and zinc have been found to have protective, anti-inflammatory, and antioxidative effects in patients with AD. Also of note, probiotics can be a powerful tool for patients with AD, as they can help modulate the gut and cutaneous microbiome, which in turn can reduce allergic response and AD severity (Rusu et al., 2019).

Aside from diet and nutrients, which can be argued to be the most viable factors that AD patients can control in their own lives, another set of factors that can have influence include the external environment where one resides, climate, and lifestyle factors such as sleep and stress. For AD patients with compromised skin barriers, the physical environment can be extremely impactful. Urban environments may worsen AD more than rural ones due the presence of pollutants, difference in diets, and overall exposure to certain exogenous toxins (Sriyaraj, Priest, & Shutes, 2008). Climate also plays a role, with higher temperatures, humidity, and UV light typically correlating to lower AD prevalence (Silverberg, Hanfin, & Simpson, 2013). However, contradictory evidence exists, suggesting that perspiration caused by these factors can serve as an irritant (Sargen, Hoffstad, & Margolis, 2014). The

relationship between the environment and AD is intricate and seems to require individuals to be intentional in gaining the benefits from their environment, without overdoing it and causing worsened symptoms. This type of cyclical pattern, where AD symptoms may prevent patients from doing the thing that could help them improve their symptoms also exists in terms of lifestyle, specifically with sleep. Over 60% of AD patients report sleep disturbances caused by itching and soreness, and at the same time, AD seems to flare more after a night of poor sleep (Chang & Chiang, 2018; Lewis-Jones, 2006). While some studies have suggested small dosages of valerian root and melatonin to aid in sleep, the research is limited and must be investigated further in AD-specific populations (Chang et al., 2016; Shinjyo et al., 2020). Related to sleep is the idea of stress, which has certain effects on the immune system that may in turn affect AD. Stress reduction strategies may include psychological or relaxation interventions such as various forms of cognitive therapy, hypnosis, massage, meditation, and mindfulness, as well as exercise. Interestingly, joy, music, and laughter also play a role, as positive emotions have the ability to mitigate both psychological and physiological stress (Solomon et al., 2018). Overall, patients with AD should aim to prioritize their sleep and manage their stress, as both can contribute significantly to disease flares.

In assessing all of these dietary, lifestyle, and emotional factors in one paper (see *Figure 5*), the current review aims to identify all the meaningful factors that AD patients should consider in crafting their individualized treatment plan. In the case of AD, there is no magic one-size-fits-all solution, but rather a combination of changes patients should make, over time, in order to help themselves gradually heal. The goal of this review is not to insist that patients change their entire lives at once. Instead, it seeks to inspire patients with information to help them take control of their AD, a condition which seems to have a mind of its own at times. When patients start to be mindful about the interplay between the way they live their lives and their AD, they become aware of just how much they can do to help themselves. Much of the literature that currently exists only examines one or a few of these factors, but putting them all together gives patients a sort of road map which they can use as a guide. From modifying diet, investigating their nutrient deficiencies, sleeping more, and managing stress, to trying alternative options like herbal remedies and acupuncture, this review seeks to empower patients with the holistic options they have to improve their AD and lives.

Figure 5. *AD protective and risk factors.*



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