Review

How lifestyle factors and their associated pathogenetic mechanisms impact psoriasis

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SUMMARY

Backgrounds and aims: Psoriasis is a skin disorder affecting approximately 2−3% of the global population. While research has revealed a strong genetic component, there are few studies exploring the extent to which lifestyle factors influence psoriasis pathogenesis. The aim of this review was to describe the role of lifestyle factors as both a potential cause and treatment for psoriasis. The review also examines the underlying mechanisms through which these lifestyle factors may operate.
Methods: This narrative review aims to incorporate current knowledge relating to both lifestyle and pathogenetic factors that contribute to and alleviate psoriasis presentation. Studies reporting the effect of an inflammatory diet and potential dietary benefits are reported, as well as insights into the effects of stress, smoking and alcohol, insulin resistance and exercise.
Results: Poor nutrition and low Omega 3 fatty acid intake, likely combined with fat malabsorption caused by gut dysbiosis and systemic inflammation, are associated with psoriasis. The data strongly suggest that improvements to disease severity can be made through dietary and lifestyle interventions and increased physical activity. Less conclusive, although worthy of mention, is the beneficial effect of bile acid supplementation.
Conclusions: Lifestyle interventions are a promising treatment for psoriasis and its associated co-morbidities. However, gaps and inadequacies exist within the literature, e.g. methodology, absence of a unified scoring system, lack of controlled clinical data and lack of studies without simultaneous usage of biologics or alternative therapies. Future directions should focus on high quality cohort studies and clinical trials.

1. Background and aims

Psoriasis is thought to be the most common autoimmune disease in America [1] and as many as 180 million people suffer from psoriasis worldwide [2]. It has a well-documented emotional and social burden, capable of significantly impairing an individual's quality of life [3]. The skin typically presents with well-defined red lesions, white scales and epidermal thickening. This occurs most commonly on the knees, elbows, scalp and lower back area [4] and is frequently accompanied by itching or pain [3]. Psoriasis onset manifests in two distinct age peaks: 19 and 58.5 years old, with some variation observed between males and females [5]. Psoriasis also has a proven genetic link [6,7]. Almost half of early-onset psoriatics' parents (mother or father) were also found to suffer from psoriasis, a trend which was not observed in late-onset subjects [5]. Although the visible nature of psoriasis symptoms makes it easy to assume that the condition extends only to the skin's surface, it is, in fact, more accurate to consider it as a representation of chronic inflammation, mediated by a dysfunctional immune system. Figure 1 demonstrates the extensive involvement of the

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Abbreviations

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BMI	body mass index
CD	cluster of differentiation
COX	cyclooxygenase
cPLA2	cytosolic phospholipase A2
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
DAMP	damage-associated molecular protein
EPA	eicosapentaenoic acid
DAPSA	Disease Activity in Psoriatic Arthritis
DGLA	dihomo-gamma linolenic acid
DHA	docosahexaenoic acid
FODMAPs	Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols
FXR	farnesoid X receptor
GLA	gamma linolenic acid
GLUT	glucose transporter
HDL	high density lipoprotein
HETE	hydroxy-eicosatetraenoic acid
HODE	hydroxyoctadecadienoic acid
HPA	Hypothalamic-Pituitary-Adrenal
HSD	hydroxysteroid dehydrogenase
IFN	interferon
IgA	immunoglobulin A
IL	interleukin
IRS	insulin receptor substrate
JAK-STAT	Janus Kinase-Signal Transducer and Activator of Transcription
LDL	low density lipoprotein
LOX	lipoxygenase
LPS	lipopolysaccharides
LysoPL	lysophospholipid
MAPK	mitogen activated protein kinase
MDA	Minimal Disease Activity
MET	metabolic equivalent of task
NF	nuclear factor
NK	natural killer
PAMP	pathogen-associated molecular protein
PASI	psoriasis area severity index
PKC	protein kinase C
PPAR	peroxisome proliferator activated receptor
PRRs	pattern recognition receptors
PUFA	polyunsaturated fatty acid
RAS	renin-angiotensin system
RNA	ribonucleic acid
ROS	reactive oxygen species
SIBO	small intestinal bacterial overgrowth
sPLA2	secretory phospholipase A2
STAT	signal transducer and activator of transcription
Th	T helper
TLRs	toll-like receptors
TNF	tumour necrosis factor
Tregs	regulatory T cells
UV	Ultraviolet
VEGF	vascular endothelial growth factor
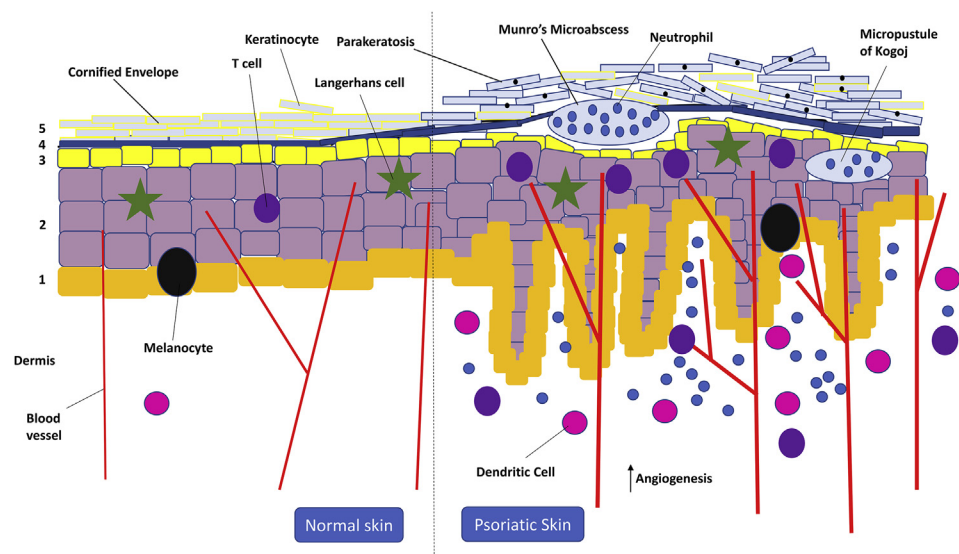
Fig. 1. Diagram of normal skin *vs.* psoriatic skin. The epidermis (1-5) consists of the *stratum basale* (1), the *stratum spinosum* (2), the *stratum granulosum* (3), the *stratum lucidum* (4) and the *stratum corneum* (5). Keratinocytes, which are the predominant cell in the epidermis, are formed in the *stratum basale*. Normally, keratinocytes gradually push upwards in response to desquamation at the skin's surface. Psoriatic skin is characterised by a thinning epidermal layer, a diminished *stratum granulosum* and elongated ridges or retes. Accelerated keratinocyte migration results in Parakeratosis, where nuclei are still present in the *stratum corneum*. Munro's Microabscesses and Micropustules of Kogoj are characteristic features of psoriasis and develop following mass infiltration of neutrophils, particularly following increased angiogenesis.

immune system in psoriasis presentation and the evident disruption both above and below the skin's surface. Furthermore, psoriasis has an association with other systemic comorbidities such as cardiovascular disease, metabolic syndrome, Crohn's disease and non-alcoholic fatty liver disease [3].

Despite the multitude of psoriasis-related articles (currently, *Pubmed* > 45,000), there exists a disconnect between its causation and its pathogenesis. This is facilitated by a lack of understanding of autoimmune inflammatory conditions as a whole and also due to the lack of replicable pathology in animal models. A 2016 Global

Report on Psoriasis, conducted by the World Health Organisation (WHO), emphasised the importance of conducting research into the causes of psoriasis, developing new treatments and improving knowledge amongst health-care practitioners [3]. However, treatment for psoriasis still revolves around symptomatic improvement through the use of biologic agents, both topical and systemic. Many of these treatments can provide relief from psoriasis, through their regulation of keratinocyte proliferation and T-cell activation, but may preclude long-term usage. For example, immunosuppressants such as methylprednisolone and methotrexate are frequently used to treat severe psoriasis despite evidence of worsening following withdrawal [8], also referred to as the 'rebound effect.' However, treatment is primarily determined by psoriasis severity and other regimens such as vitamin D analogues, salicylic acid and keratolytics have demonstrated effectiveness, particularly when combined with other therapies [9]. A significant financial burden must also be considered, with total estimated treatment costs in the U.S. thought to be in excess of $3 billion per year [10]. There is increasing interest in recommending lifestyle modifications which may produce standalone benefits amongst sufferers. Certainly, evidence is accumulating that by incorporating food components such as Omega-3 polyunsaturated fatty acids or by adopting whole-diet approaches [11,12] psoriasis severity can be decreased. Despite this, and an apparent willingness by psoriatics to modify their diet, only a relatively small number seem to discuss such changes with their dermatologist [11]. Accordingly, this review aims to present the evidence linking lifestyle factors with psoriasis and will also investigate the underlying associated pathogenetic mechanisms. This is vital to facilitate a holistic treatment plan amongst health-care providers and to ensure consideration of a best practice approach for the individual.

1.1. Methods

Given the prevalence of psoriasis worldwide and its associated high healthcare costs, this review will explore the nutritional and lifestyle interventions, which have been used in its treatment. This is a narrative review which incorporates studies that demonstrate known effects of an inflammatory diet and poor lifestyle on psoriasis pathogenesis and its association with underlying pathogenetic mechanisms. These studies were retrieved from *PubMed,* using the search term "Inflammatory AND Diet AND Psoriasis". All study types were considered due to a lack of available data. Clinical trials investigating the beneficial effects of diet, whilst excluding drug treatment, were retrieved from *PubMed* using the search term "Diet AND Psoriasis". Search terms, pertaining specifically to "psoriasis" and incorporating the Boolean "AND", using *PubMed,* included: bile acid supplementation; Omega-3 fatty acids; stress; small intestinal bacterial overgrowth/SIBO; nutrition/diet; lifestyle; inflammation; Hypothalamic-Pituitary-Adrenal (HPA) axis; paneth cell dysfunction; coeliac; eicosanoid; lipopolysaccharides/endotoxins; treatment; smoking and alcohol; vitamin D. Manual searches for specific authors and journals that have published related research were also conducted.

2. Results

2.1. Pathogenetic mechanisms

2.1.1. Essential fatty acid metabolism and the eicosanoids

Fatty Acids play an important part in intracellular signalling by facilitating transcription factors and gene expression [13]. They are also essential for the formation of skin structure and maintaining homeostasis [14]. The essential fatty acids are so-named as they must be obtained from dietary sources and cannot be produced within the body. Endogenous conversion of alpha-linolenic acid to its longer chain derivatives is possible but initial dietary input from alpha-linolenic acid is required. The few articles documenting the importance of essential fatty acids fail to mention the seminal works of Burr and Burr [15,16], who conducted a series of dietary studies on rats. Rats fed a fat-free diet soon developed scaling and inflammation of their skin, thus demonstrating the importance of diet with epidermal homeostasis. Essential fatty acids, alpha-linolenic acid (n-3) and linoleic acid (n-6) are desaturated and elongated using the same enzymes however, under normal circumstances, Omega 3 is selectively incorporated into immune cells and cell membranes in place of Omega 6 [13]. As a result of Western Diet consumption, which greatly alters the ratio of Omega 6 to Omega 3 fatty acids, most polyunsaturated fatty acids (PUFAs) derive from Omega 6 sources.

Eicosanoids are lipid intermediaries which form the connection between immune cells and dietary fatty acids [17] through their ability to regulate inflammation. They are the oxidised derivatives of 20-carbon PUFAs [18] such as arachidonic acid and eicosapentaenoic acid (EPA) (see Fig. 2). Increased incorporation of both EPA and docosahexaenoic acid (DHA) into membranes results in less arachidonic acid eicosanoids being produced [13] and DHA has been shown to have a suppressive effect on antigen presenting cells in the epidermis [19]. However, the consequences of a Western Diet mean that eicosanoids are mostly produced from arachidonic acid substrates [20], which results in increased inflammation. Arachidonic acid has a particularly potent pro-inflammatory effect due to its three activated CH_2 groups, rendering it susceptible to oxidative attack and more likely to form free radicals [21]. Eicosanoids such as prostaglandins and leukotrienes develop a variable structure depending on the PUFA from which they were generated [20]. This potentially confers the mechanism by which arachidonic acid promotes inflammation, whilst EPA alleviates it [20].

Non-enzymatic production of eicosanoids (i.e. not derived from lipoxygenase (LOX) or cyclooxygenase (COX) etc.) is thought to result from an overabundance of free PUFAs [21]. PUFAs have a higher incidence of double bonds, rendering them more susceptible to free radical damage, thus creating an opportunity for increased membrane damage [22]. Following eventual enzyme deactivation there is a switch to enzyme-independent production and increased free radicals can be produced, allowing for the state of oxidative stress observed in psoriasis and other inflammatory conditions [21].

Linoleic acid is an important component of fatty acids in the skin and assists in maintaining the epidermal barrier [14]. *In vitro* experiments [23] have shown that linoleic acid combined with 15-LOX produces the metabolites 13-HODE (Hydroxyoctadecadienoic acid) and, to a lesser extent, 9-HODE (see Fig. 2 above). Ziboh and colleagues observed an increase in 13-HODE following corn oil feeding in guinea pigs and found that 13-HODE diacylglycerol can selectively inhibit protein kinase C (PKC)-β activity [23]. This can affect hyperproliferation and differentiation at the epidermal level [23] and competitively inhibits from the production of arachidonic acid leukotrienes, thus preventing the production of inflammatory mediators. A double-blind, randomised, placebo-controlled trial tested the efficacy of a PKC inhibitor on psoriasis [24] and found that after two weeks of treatment, keratinocyte proliferation, epidermal thickness and T cell involvement were reduced. Similarly EPA and DHA can also inhibit PKC activity and nuclear factor (NF)-κβ activation from free arachidonic acid [25].

Leukotrienes function as potent chemoattractants and also encourage leukocyte adhesion to endothelial cells [26]. The importance of leukotriene B4, which is produced from arachidonic acid and 5-LOX, for intracellular communication and neutrophil activation and infiltration has been demonstrated in *in vivo* mouse
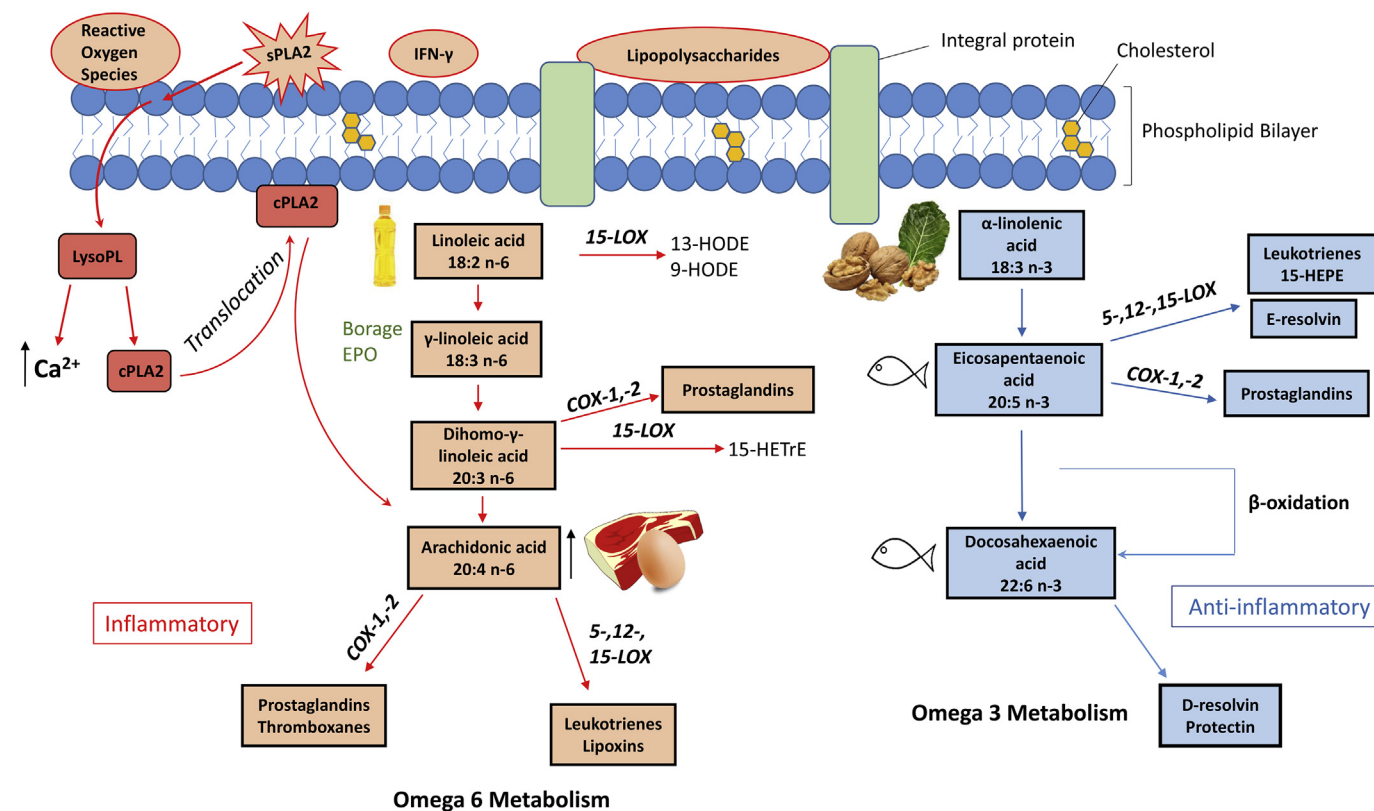
Fig. 2. A simplified version of Omega 6 and Omega 3 metabolism. Inflammatory mediators such as lipopolysaccharides, interferon-γ (IFN-γ), reactive oxygen species and cell injury lead to the production of secretory phospholipase A2 (sPLA2). This results in the release of pro-inflammatory lysophospholipid (LysoPL), increased Ca^{2+} and cytosolic phospholipase A2 (cPLA2). cPLA2 is translocated to the phospholipid membrane where it incites the release of arachidonic acid and results in eicosanoid production. Most eicosanoids are produced from arachidonic acid in a Western Diet.

models [27]. Inhibition of leukotriene B4 demonstrated significant psoriasis improvement compared with controls in one double-blind randomised clinical study [28]. Furthermore, heightened levels of both arachidonic acid and leukotriene B4 have been observed in psoriatic skin [29]. EPA acts as a substrate for leukotriene B5, which opposes the effects of arachidonic acid-derived leukotriene B4 [25]. Treating psoriasis nutritionally with DGLA, GLA and EPA is being explored, with the aim of reducing inflammatory arachidonic acid eicosanoids such as 12-HETE, which are commonly found in lesioned psoriatic skin [14].

Psoriasis is characterised by infiltrating cluster of differentiation (CD)4+ (primarily T helper (Th)1 and Th17 cells), CD8+ T cells [30] and, especially, aggregating neutrophils in the epidermis [20] (see Fig. 1). Animal models have revealed that by altering fatty acid balance within the diet, it is possible to change the composition of immune cells [13]. One study revealed that ingestion of Omega 3 fatty acids from fish oil was associated with a larger decrease of interleukin (IL)-2 production and a decreased Th1 response compared to a diet rich in Omega 6 or saturated fatty acids [31]. The authors concluded that dietary long-chain Omega 3 fatty acids have the ability to affect genetic expression, perhaps by encouraging movement away from a polarised Th1 response [31]. This is of importance, as observed in a renin-angiotensin system (RAS) murine-model which found that suppression of IFN-γ, a Th1 cytokine, led to decreased neutrophil infiltration and keratinocyte proliferation in the skin [30].

CD36 has also been implicated in altering lipid metabolism, following consumption of a high-fat diet [32]. In fact, both CD36 and Glucose Transporter (GLUT) 4 are used by the body, following insulin stimulation, to increase fatty acid and glucose uptake by the cell [32]. Expression of CD36, which is increased in psoriasis [33], is regulated by peroxisome proliferator activated receptors (PPARs) [32], of which there are three isoforms. Fatty acids and eicosanoids are thought to work in tandem with the PPARs [32]. Hydroxylated fatty acids (e.g. 12-HETE) aggregate in affected psoriatic skin and assist PPAR-β/δ activity [33]. Conversely, PPAR-α is thought to attenuate inflammatory genes and its expression is decreased in psoriasis, notably following UVB exposure [34]. Upregulation of PPAR-α leads to antioxidant enzyme production, which helps alleviate the effects of oxidative stress [34]. The isoforms PPAR-β/δ work in the opposite manner and are enhanced in involved psoriatic skin [2]. They seem to induce the phosphorylation of signal transducer and activator of transcription (STAT)3, thus leading to progressive inflammation [35] and the abnormal differentiation observed in psoriatic keratinocytes [2]. Furthermore, activation of STAT3 in adipose tissue has been demonstrated to encourage fatty acid oxidation [32].

2.1.2. Metabolic syndrome

One of the most widely used definitions of metabolic syndrome was devised by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III [36]. A diagnosis of metabolic syndrome can be made when three out of five of the following criteria are met: increased fasting blood sugar levels; hypertension; a higher waist circumference; lowered high density lipoprotein (HDL) cholesterol levels and hypertriglyceridaemia (see Huang, 2009, for more details) [36]. This is particularly noteworthy as psoriasis is frequently associated with higher levels of obesity; diabetes or insulin resistance and serum lipids, such as triglycerides and total cholesterol [3]. Furthermore, increased prevalence of

metabolic syndrome has been observed in psoriatics versus controls [37]. Additionally, although no significant difference was observed in body weight between psoriatic patients and controls, they did have a significant increase in overall fat mass *vs* controls (p < 0.001) in one observational study [12]. Recent observational data from the UK Biobank and the Nord-Trøndelag Health Study (HUNT) in Norway found an average body mass index (BMI) difference of 1.26 kg/m^2 between adult psoriasis patients and controls and additionally revealed a causal relationship between BMI and psoriasis [38]. Evidence for this relationship has been further strengthened with recent uncontrolled clinical trial evidence demonstrating a positive correlation between disease severity in psoriatic arthritis sufferers and BMI [39]. Waist circumference, which is correlated with visceral fat, also has a demonstrated association with psoriasis [12]. 13−34% of plaque psoriasis cases are positively correlated with obesity [40], as are increases in BMI and waist-to-hip ratios [41]. The importance of obesity as a risk factor for psoriasis [42] is clear: each unit increase in BMI was associated with a reported 9% increased risk for psoriasis onset [12,38]. Obesity has also been shown to impair the efficacy of treatment for psoriasis [43]. However, this association is likely the result of a two-way relationship, whereby psoriasis is more likely to manifest in obese individuals and the dysfunctional metabolism of obesity predisposes those individuals to psoriasis [12].

Most adipose tissue is composed of adipocytes containing a vacuole filled with triacylglycerides [44] however, it also contains a stromovascular fraction [45] which is considered to be very metabolically active and capable of producing numerous adipokines [44]. Adipokines consist of hormones such as adiponectin and leptin; cytokines such as tumour necrosis factor (TNF)-α and IL-1β; prostaglandins; growth factors such as vascular endothelial growth factor (VEGF) and various chemoattractants [44]. Adipocytes and, in particular, stromal vascular cells seem to propagate their own inflammatory status by acting as both the origin and target of proinflammatory signalling [46]. Obesity is characterised by the deregulation of the endocrine function of adipocytes, which leads to a decrease in adiponectin secretion and an increase in leptin secretion [44]. Importantly, these altered hormone states are also mirrored in psoriatics [47]. Adiponectin has an antagonistic effect on TNF-α, meaning its decreased production in psoriatics could mediate the synthesis of TNF-α [47]. Leptin reduces T-cell regulation [48], induces the secretion of chemoattractants within psoriatic skin [49] and is thought to induce inflammation and endothelial dysfunction [44].

Insulin plays an important role in maintaining homeostasis in the skin by balancing new keratinocyte development in the *stratum basale* with desquamation in the *stratum corneum* [50]. This balance is undone in the case of chronic inflammatory conditions like psoriasis, whereby a proliferation of inflammatory cytokines, acting through the mitogen activated protein kinase (MAPK) pathway, cause the degradation of IRS-1 [50]. This leads to the abnormal differentiation associated with psoriasis, insulin resistance and other comorbidities. The MAPK pathway, which is enhanced in affected psoriatic skin [30], is upregulated by pro-inflammatory cytokine transcription factors such as IL-1β [51] and has been observed to create similar psoriatic pathologies in transgenic mice [30]. For a more complete overview of the cytokines associated with psoriasis development, see Table S1.

Certain pro-inflammatory cytokines, such as TNF-α and IL-1β, are capable of contributing to insulin resistance and are associated with psoriasis pathogenesis. The presence of TNF-α causes a preferential serine-phosphorylation of IRS-1, in place of tyrosine. This induces a conformational change, which renders IRS-1 less capable of binding with insulin receptors [52]. TNF-α has also been shown to reduce GLUT 4 protein levels *in vitro* and produced a 30−40%

inhibition of glucose uptake by cells following insulin incitation [53]. Interestingly, a study by the *American Heart Association*, which induced insulin resistance in rat cells through aldosterone administration, found that antioxidants prevented the breakdown of IRS-1; whereas reactive oxygen species (ROS) and tyrosine kinases and phosphoinositide-dependent kinase enhance its deterioration [54]. Inhibition of TNF-α generates an increase in HDL cholesterol levels and blood insulin levels [2]. It was shown by Buerger and colleagues that induction of insulin resistance, *via* IL-1β, inhibits insulin-controlled keratinocyte differentiation and thus confers the pathway through which late onset psoriasis might progress [51,55]. Recalling that 58.5 years is one of the two distinct age peaks for the onset of psoriasis [5], it is worthy of mention that adults between the ages of 45 and 64 have a considerably greater rate of diagnosis for diabetes [56].

2.1.3. The gut connection

The gut wall consists of mucus-covered epithelial cells joined by tight junctions and forms a protective barrier between the bloodstream and bacteria. It is further organised into crypts, villi and microvilli. Paneth cells are found at the base of these crypts and produce bactericidal granules e.g. lysozyme [57]. Paneth cell dysfunction may be a potential mechanism for increased intestinal permeability and tight junction disruption. A small study investigating the correlation between psoriasis development and intestinal dysfunction found significantly higher incidence (P < 0.05) of intestinal permeability in subjects with psoriasis compared to healthy controls, irrespective of psoriasis severity [58]. Additionally, application of a regimented diet and improvement to the digestive system does have scientific merit for rectifying psoriasis-associated abnormalities [6,59]. Coeliac disease has been observed to have a higher prevalence among psoriatics versus controls, P < 0.0001 [6] and, furthermore, antigliadin antibody IgA was shown to be present at higher levels in psoriatic patients when compared with controls, P < 0.05 [60]. It has been proposed that this association is mediated by either a genetic component or *via* abnormal intestinal barrier function [6].

The gastrointestinal microbiota performs many important roles within the body: it produces secondary bile acids [59], thereby assisting in fat metabolism; it aids the development of the immune system; it helps with vitamin synthesis [61] and it competes against pathogens for adhesion sites. This creates and maintains intestinal homeostasis. However, inflammation of the intestines and poor diet can contribute to alteration of the microbiota composition [59]. Small intestinal bacterial overgrowth (SIBO) is a gastrointestinal condition distinguished by a proliferation of pathogenic bacteria residing in the small intestine. It is characterised by a lowered villous to crypt ratio and is a common cause of undiagnosed malnutrition, particularly in the elderly [62]. Whilst there is a scarcity of studies relating to SIBO and psoriasis, there are numerous mentions of lipopolysaccharide and psoriasis in the literature [63−65]. The Western Diet generates increased lipopolysaccharide levels [66] and inflammatory eicosanoids [13] which could mediate psoriasis pathogenesis.

Lipopolysaccharide (LPS) or endotoxin are derived from gram-negative bacteria and act as Pathogen-Associated Molecular Patterns (PAMPs) [67] that bind to Pattern Recognition Receptors (PRRs), e.g. Toll-like receptors (TLRs), on immune cells to stimulate pro-inflammatory cytokine responses. Higher LPS binding protein levels, which correlate to serum levels of LPS, were observed in psoriatics that demonstrated signs of metabolic syndrome [65]. LPS can also be defined as damage-associated molecular patterns (DAMPs) due to its damage-inducing endotoxic effect [68]. Endotoxin excess leads to the development of chronic low-grade inflammation, which can have system-wide effects [66]. Increases

can be determined by diet, for example a combination of high fat (type not specified) and sucrose generated elevated LPS levels and reduced occludin in rats [66]. Occludin is a transmembrane protein which regulates epithelial tight junctions [69]. Mice treated with LPS were shown to demonstrate occludin disruption and relocation caused by TNF, resulting in increased intestinal permeability [70]. Moreover, increased intestinal permeability leads to bacterial translocation across the gut, raised LPS levels in the bloodstream and contributes to systemic inflammation [66].

As discussed in section 2.1.1, psoriasis aetiology is typically thought to result from disturbances to lipid metabolism [2]. The dysbiosis observed in SIBO is capable of increasing the bacterial deconjugation of bile acids which leads to fat malabsorption [71]. This can develop into a decline in fat-soluble vitamins and altered T-cell function [71]. The increase of unconjugated bile acids causes a rise in integral membrane protein dissociation, which creates a further increase in intestinal permeability [72]. SIBO [73] and endotoxins [63–65] have been linked to psoriasis development, however details of its pathogenesis require further research.

Peroxisome metabolism could be the link between nutrition, endotoxins and psoriasis generation. Peroxisomes are involved in the breakdown of hydrogen peroxide to water, eicosanoid production and synthesis of bile acids and cholesterol [74]. LPS is capable of inducing TNF-α and IL-8 mRNA expression in normal keratinocytes [75] and both LPS and TNF-α are capable of initiating dysfunctional peroxisomal β-oxidation in rat livers [74]. Furthermore, endotoxin administration has been observed to significantly alter the fatty acids in peroxisomes, particularly with regard to phospholipid and cholesterol composition [74]. Animal models have shown that treatment with endotoxins resulted in abnormal cholesterol transport [76]. HDL cholesterol function was impaired, rendering it less able to remove cholesterol from macrophage carriers. This same abnormality was observed in psoriatics and may be associated with the increased presence of HDL cholesterol autoantibodies [77].

2.2. Lifestyle

2.2.1. The stress response

Although the connection between psoriasis and stress is well-documented [78,79], it is not straightforward. In one study, baseline and cortisol measurements taken following application of an acute social stress [80] revealed differing results depending on a patient's stress responsiveness. Psoriatics that were more stress-responsive had a significantly higher Psoriasis Area Severity Index (PASI) score, $P < 0.01$, compared to their less-responsive counterparts. They also demonstrated significantly lower basal levels of salivary cortisol, $P < 0.01$, and serum cortisol, $P < 0.016$, following a social stress test relative to non-stress responsive psoriatics. Control evaluation revealed a significant association between pulse rate and serum cortisol following stress application, $P < 0.05$, which was not observed in either psoriatic group. The study seems indicative that psoriasis pathogenesis is exacerbated in a hypocortisolaemic state and, consequently, that stress-responsive psoriasis is linked with Hypothalamic-Pituitary-Adrenal (HPA) axis dysfunction.

Lin et al. hypothesised that acute stresses are of some benefit for the prevention of inflammatory disease due to the resulting increase in glucocorticoid production [81]. The authors demonstrated reduced cutaneous inflammation following an induced stress in their mouse model. However, perhaps acute stresses administered to psoriatics who demonstrate abnormal HPA-axis function due to chronic stress are unable to produce an appropriate response. This scenario would be more in line with the findings of Richards and colleagues [80]. An acute stress response may also manifest abnormally in psoriatics, as a pre-existing elevation of baseline inflammation could predispose them to a response more associated with chronic stress.

Keratinocytes do contain adrenergic receptors and are capable of producing adrenaline locally [78]. Adrenaline production leads to an eventual rise in intracellular calcium concentration, which can control epidermal development [78]. The skin contains all the necessary components to act as a local version of the HPA axis [82] and can, therefore, be regarded as a neuroendocrine organ. Normal skin cells are capable of producing cortisol locally via 11β-Hydroxysteroid Dehydrogenase (HSD)1 activation from cortisone [82,83] within the endoplasmic reticulum [83]. This is thought to contribute to homeostasis in the skin by negating the effect of continuous disruption to the skin's barrier functions [83]. 11β-HSD1 is decreased in psoriatic lesions compared to unaffected skin, causing increased keratinocyte proliferation and lowered cortisol production [84].

Usually, glucocorticoid receptors are present in the skin [82] and are localised in the nuclei [85]. However, VEGF and IFN-γ prevent receptor translocation from the cytoplasm to the nucleus in psoriatic keratinocytes [85]. Inactivation of glucocorticoid receptors impedes the immunoregulatory response of glucocorticoids [86]. Notably, this response is dose dependent and both corticosterone and cortisol have been observed to have immunosuppressive effects at high concentrations and immune-enhancing effects at low concentrations [86]. This, perhaps, implies that low cortisol levels could help mediate the chronic inflammation present in psoriasis. In fact, low cortisol levels combined with stressful events are thought to promote the development of free radicals in psoriatics [87].

Evers and colleagues observed that psoriatics had lower average cortisol levels when subjected to continuously high levels of stress in their longitudinal study [88]. The HPA axis will normally produce corticotropin-releasing hormone (CRH) following prolonged stress, ultimately leading to the production of cortisol [78]. Skin cells, in particular the melanocytes, are also capable of producing CRH [78] and its receptors locally [89]. CRH has recently been implicated in the regulation of keratinocyte proliferation [83]. This is notable because increased levels of serum CRH [82] and reduced CRH expression in the skin [90] have been observed in cases of psoriasis with a PASI>10. Decreased CRH Receptor mRNA expression was also found in psoriatic lesioned skin samples compared to controls [90], perhaps due to a feedback loop created by the high serum CRH [90].

Psychological stress induction was observed to significantly increase the number of cutaneous lymphocyte-associated antigen+ natural killer (NK) cells in the circulation of psoriatics [79]. It is thought that these cells may induce skin homing [79], potentially augmenting disease severity following a stress. A concurrent prospective study by Verhoeven and colleagues, found increased severity of psoriasis four weeks after a period of high stress [91]. However, delayed onset of affliction is variable and can take from two days up to a month [10].

2.2.2. The inflammatory diet

Typically, research concerning diet and psoriasis concentrates on the prevention of inflammation. There are very few studies regarding the constitution of a pro-inflammatory diet and its connection to the development of psoriasis, although it is usually synonymous with a 'Western' Diet, i.e., one that is high in sugar, starches, processed meat and saturated fat, and low in beneficial foods like fruit, vegetables and Omega 3 fatty acids. The Western Diet promotes the development of chronic inflammation by decreasing insulin sensitivity and increasing adiposity, resulting in augmented inflammatory cytokines. A period of high-fat feeding (type not specified) was shown to lead to a decline of 11β-HSD1 in

both rats and mice [92,93], suggesting that dietary intake could affect local cortisol production in the skin. In addition, high consumption of *trans* fatty acids is linked to an increase in C-reactive protein (CRP) [94], a non-specific marker of inflammation which is correlated with disease severity in psoriasis [95].

Table 1 [96–106] consists of a mini-review of inflammatory diet factors and psoriasis. The literature is lacking in clinical trial data, however poor nutrition; low intake of Omega 3 fatty acids and diet composition do have an association with psoriasis. In fact, the murine model cross-sectional study conducted by Qin et al. [104], documented in Table 1 below, strongly suggests that altering the dietary ratio of Omega 3 to Omega 6 may benefit a range of systemic conditions, provided these same findings can translate to human patients. A number of reviews have highlighted nutrition and diet as a means of either triggering or improving psoriasis [96,100–102,105], however no cohort studies have been found.

Simopoulos has conducted a number of studies [107–109] articulating the detrimental effects of a diet with a one-sided Omega 6 to 3 ratio. Western diets, which have a ratio of approximately 20:1, have been implicated in a number of chronic inflammatory conditions such as cardiovascular disease, cancer and autoimmune conditions [108]. Conversely, a ratio closer to 1 has been shown to alleviate inflammation, mortality and irregular cell proliferation in a number of disorders [107]. Notably, mixed results have been observed in clinical trials treating type 2 diabetes, obesity [109] and psoriasis itself using Omega 3 fatty acids.

2.2.3. Smoking and alcohol

A direct causation between psoriasis and smoking is difficult to ascertain due to lack of clinical trial data, although collated data suggest increased incidence and risk of psoriasis in smokers *vs.* non-smokers [110] and meta-analysis of prevalence studies found an association between psoriasis, current smoking and former smoking [111]. A case–control study, examining new cases of plaque psoriasis (n = 373), associated smoking with a 70% increased risk for development of psoriasis but was not associated with increased severity [112]. A majority of studies do reveal that smoking worsens psoriasis severity, using PASI scoring as a measurement [110,113]. Smoking is thought to worsen or initiate psoriasis pathogenesis by producing free radicals, which have a deleterious effect through their activation of the MAPK, NF-κβ and Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathways [110]. It damages skin directly by increasing ROS formation and decreasing protective antioxidant gene expression

[114]. In addition, superoxide and hydrogen peroxide are increased in psoriatic skin [114], resulting in a skewed antioxidant to free radical ratio. This altered ratio is also observed between smokers and non-smokers [114] and the effect may be compounded in psoriatic skin. Nicotine enhances IL-12 production in dendritic cells and further activates innate immune system defences such as macrophages and natural killer cells [114]. It upregulates CD40 and CD86 expression, which are necessary for T-cell activation [110] and induces macrophage production of IL-1β and TNF-α [114]. VEGF, which is elevated in smokers, has been demonstrated to produce a similar psoriatic pathology in transgenic mice [114].

Alcohol consumption has been observed to interfere with the efficacy of psoriatic treatment and chronic alcohol consumption has been noted to induce inflammation by upregulating CD80 and CD86 expression, leading to enhanced T-cell activation [115]. Furthermore; patients with chronic alcohol-related diseases, such as alcoholic liver disease, produce increased TNF-α, leading to higher numbers of macrophages, monocytes and TNF-α converting enzyme expression [115]. It has also been proposed that ethanol excreted by exocrine glands could serve to disrupt the skin barrier leading to keratinocyte hyperproliferation [115]. Occasional alcohol consumption appears to have an opposite effect by facilitating immunosuppression [116] although, interestingly, this could actually induce psoriasis onset by facilitating streptococcal infection, a known trigger for psoriasis [115]. Brenaut et al. revealed a definite association between alcohol consumption and psoriasis risk in their systematic review, however they conservatively concluded that there was insufficient evidence to signify a direct risk, as many of the included studies did not assess alcohol consumption prior to psoriasis onset [117]. Despite this, one prospective cohort study and three case control studies indicate that alcohol consumption is a risk factor for psoriasis [117]. Removal of alcohol was also the most effective dietary behaviour change employed by respondents to a national survey (251 out of 462), conducted by Afifi et al. in the U.S. [11]. However, the survey does not report on simultaneous usage of alternative treatments, such as Methotrexate which recommends alcohol cessation. It should be considered that alcohol consumption can lead to a positive energy balance and thus may indirectly lead to increased visceral fat, which is also positively correlated with psoriasis [118].

2.2.4. The immunomodulatory benefits of exercise

Observations in the cohort study by Frankel et al. revealed that a reduced risk for psoriasis corresponded with increased physical

Table 1
Review of *Pubmed* results for "Inflammatory AND Diet AND Psoriasis". All study types, excluding reviews, were considered due to lack of available data. The Boolean "AND" was used to narrow the search relating to an inflammatory diet and psoriasis. A number of older and irrelevant articles were excluded, leaving 6 studies.

Study	Study Type	Factor(s)	Conclusion
Vasseur et al., 2016 [97]	Murine model. Controlled cross sectional	High fat diet (type unspecified)	Presentation of psoriasiform dermatitis was exacerbated in mice fed a high fat diet compared to those fed a standard diet (type unspecified). High fat mice also developed non-alcoholic steatohepatitis. Heightened inflammation was accompanied by increased IL-1β, IL-17α and IL-22.
Stelzner et al., 2016 [98]	Cross sectional	Free fatty acids such as palmitic acid and oleic acid	Increased secretion of Th1 and Th17 cytokines is caused by free fatty acid stimulation of dendritic cells.
Castaldo et al., 2016 [99]	Case report	High calorie; high carbohydrate diet	Improved response to systemic therapy was observed when accompanied by a low-calorie ketogenic diet.
Khan et al., 2014 [103]	Cross sectional	Gluten	No particular association between coeliac disease and psoriasis was observed in this study (n = 80).
Qin et al., 2014 [104]	Murine model. Controlled cross sectional	Diet low in Omega 3	Transgenic mice, capable of endogenously converting Omega 6 to Omega 3, demonstrate significantly less inflammatory factors and increased numbers of T regulatory cells than control mice fed the same diet.
Ahdout et al., 2012 [106]	Case-control pilot study	Poor overall nutrition	Significantly poorer nutrition, P < 0.01, was recorded in psoriatics *vs.* controls and this may contribute to disease development

Abbreviations: IL, Interleukin; TH, T helper.

activity [119]. This finding is further supported by the cross-sectional study composed by Torres and colleagues [120] showing significantly reduced activity levels amongst psoriatics compared to controls, P < 0.001. The studies by Frankel et al. and Torres et al. did not use the PASI (Psoriasis Area Severity Index) scoring system in their studies, and neither adjusted for diet, season or *UV* exposure. A randomised controlled trial designed to assess the impact of a diet and physical activity intervention on overweight and obese psoriasis patients produced a significant improvement in psoriasis severity versus controls (information only) [121]. However, a number of patients continued to use other treatments for the duration of the study and, furthermore, almost one third of patients in the intervention arm lost weight, making it difficult to attribute PASI improvement specifically to diet or exercise. Further clinical trials should focus on identifying whether sedentary lifestyles are an independent risk factor for psoriasis and should seek to determine the impact of exercise, whilst accounting for variable confounding factors such as weight loss and alternative therapies.

Recently skeletal muscle has been descried to exhibit an autocrine and paracrine effect, in addition to its inter-tissue endocrine effects [122]. The signalling mediators have been named 'myokines' and are linked to both inflammatory and anti-inflammatory processes within the body through immune system modulation [123]. A controlled study exploring the effects of moderately exertive exercise on the immune response (n = 32) demonstrated significant attenuation of both the induction (P < 0.001) and elicitation (P < 0.05) of T-cell mediated immunity [124]. A cohort study [119] found that intense exercise was positively correlated with a lower incidence of psoriasis after adjusting for BMI. To put this in perspective, running a 15-minute mile has a Metabolic Equivalent of Task (MET) of 6.0 [125] and is classed as vigorous exercise. MET is the ratio of metabolism at rest versus activity level [125]. Walking uses approximately 2.0–3.5 MET [125] and was not shown to confer a similar benefit in the study. Running 10-minute miles for approximately 105 min per week was associated with a 25–30% lower risk of psoriasis compared with non-intensive exercise (including walking) [119].

Historically, IL-6 has been regarded as a pro-inflammatory cytokine [122,123]. In response to sepsis, it works in tandem with TNF-α [123] in immune cells to fight infection, thereby acting in a pro-inflammatory manner. Furthermore, IL-6 is increased in serum and skin lesions of psoriasis sufferers [126]. Conversely, a randomised placebo-controlled trial examining the use of *Clazakizumab*, an anti-IL6 monoclonal antibody, in patients with psoriatic arthritis did significantly improve joint symptoms but found little improvement to skin symptoms [127]. The authors surmise that although IL-6 has an important inflammatory role in joints (use of anti-IL6 agents in rheumatoid arthritis has also been met with success [126]), the mechanisms of inflammation seem to differ between patients with psoriatic arthritis and psoriasis [127]. It has been further reported that use of anti-IL6 agents can lead to psoriasis onset in patients with rheumatoid arthritis [126] and murine models are suggestive that other cytokines may offset blockage of IL-6 through excessive production in the skin [126]. Additionally, targeting IL-6 in psoriatics has revealed no benefit [128]. It has been proposed, with some controversy, that with the exception of very high intensity activity, TNF-α is not produced preceding IL-6 in response to exercise [123]. During exercise, IL-6 release increased plasma levels of IL-10 [122] which acts as an immunoregulator by decreasing the immune response to inflammatory incitation [128]. Exercising for extended periods and, in particular, running has been shown to confer the greatest benefit to IL-6 production [123]. By contrast, muscles at rest do not produce IL-6 [123].

One of the methods by which IL-10 inhibits inflammation is by blocking the effects of TNF-α, allowing cells to retain their insulin sensitivity *in vitro* [129]. A small study (n = 3) discovered that subcutaneous administration of IL-10 to psoriatic patients produced a shift towards M2 polarised macrophages, i.e. increased IL-10 production (and mRNA expression) and a reduction in IL-12 and TNF-α [130]. Macrophage polarisation and activation are largely determined by local factors such as LPS, which stimulates M1 macrophages and the release of type 1 cytokines such as TNF-α; while a local type 2 cytokine environment e.g. IL-4 and IL-13 polarises towards M2 macrophages and IL-10 release [53]. Further to this, Oliveira et al. deduced from their studies on rats that although intense exercise failed to produce a reduction of macrophage infiltration in white adipose tissue, the subsequent formation of a reduced inflammatory profile means that exercise must foster the promotion of M2 polarised macrophages [131].

2.2.5. Dietary intervention: vitamin D, omega 3 and the mediterranean diet

Clinical trial data related to diet and psoriasis is noticeably lacking, given the available evidence. The majority of studies in a search for "Diet AND Psoriasis" on *PubMed* were inadmissible due to the confounding factor of simultaneous conventional therapy. Studies reviewed focused on Omega 3 consumption; low energy diets and weight loss. Although some of the articles recommended improvement to overall diet [40,121], there were no studies solely dedicated to nutrition without weight loss as a goal. Similarly, no psoriasis-specific diet exists. This makes it difficult to deduce exact causation or extol the benefit of improved dietary choices. It is clear then, that this represents a major gap in the literature.

UV radiation is absorbed by chromophores in the skin, where it can aid vitamin D synthesis and immunosuppression [132]. Vitamin D_3 is thought to inhibit keratinocyte proliferation and inhibit T-cell proliferation [133] by adapting dendritic cell activity and activating regulatory T cells (Tregs) [134]. Vitamin D is also capable of regulating intracellular calcium levels [42] which, as discussed previously, is able to control epidermal development [78]. Topical application of vitamin D_3 was observed to down-regulate antiapoptotic protein (Bcl-xL) expression in psoriatics (n = 7) [135] and, importantly, its usage has also demonstrated similar benefit to that of corticosteroids [42]. A particularly high level of vitamin D deficiency in studies of psoriasis sufferers *vs.* healthy controls [133] has also been observed. This is irrespective of age, gender, BMI and PASI score amongst people with psoriasis and tends to worsen over winter months [133], thus corresponding to seasonal *UV* radiation exposure. *In vitro* studies have reaffirmed the importance of vitamin D concentration: low doses encouraged keratinocyte proliferation, whereas high doses prevented hyper-proliferation [42]. Vitamin D can be difficult to acquire from diet and sources are mainly derived from animal products [42]. Indeed, fatty fish and fish livers have the highest innate vitamin D concentration [42]. A placebo-controlled trial is currently underway in Norway which may provide some insight into the efficacy of oral vitamin D supplementation for psoriasis sufferers. Low levels of vitamin D are negatively associated with CRP levels [42], however recent clinical trial evidence is supportive of reverse causation: oral supplementation of vitamin D3 for two years had no significant effect on serum CRP levels in participants with osteoarthritis and vitamin D deficiency [136]. Additionally, particular care must be taken with sun exposure as the risk of nonmelanoma skin cancer increases with psoriasis severity, although this may be related to prior photochemotherapy or ciclosporin treatment [137]. Interestingly, there is cohort evidence to suggest that melanoma risk is lower in psoriasis patients when compared with controls, although no rationale is evident [137].

There is evidence to specifically suggest that a Mediterranean diet may be of benefit to psoriatics [11,12,138]. Typically, the

Mediterranean diet is composed of a range of anti-inflammatory mediators such as antioxidants, polyphenols and mono-unsaturated fats, in the form of extra virgin olive oil [12]. Low consumption of monounsaturated fat has been proposed as a potential mechanism for the increased inflammation present in psoriasis sufferers and development of metabolic syndrome on a population level [139]. Many of the dietary modifications associated with improved PASI scores, such as increased intake of fruit and vegetables [11], consumption of fish oils rich in Omega 3 [140−142] and moderate alcohol consumption [116] are also synonymous with the Mediterranean diet. A cross-sectional study (n = 62), conducted by Barrea et al. revealed a lower adherence to a Mediterranean diet for psoriasis patients versus age-, sex- and BMI-matched controls [12]. In particular, extra virgin olive oil and fish consumption had independent predictive values for psoriasis severity and CRP levels [12]. This was assessed based on the 14-item questionnaire used in the PREvención con DIeta MEDiterránea (PREDIMED) trial conducted in Spain [143]. This approach is noteworthy for providing insight into a whole-diet approach, as opposed to investigating the role played by singular dietary changes, common in studies of alternative psoriasis treatments. It should be mentioned, however, that certain dietary behaviours listed in the PREDIMED questionnaire may be incongruous to a separate survey study documenting patient-reported responses to dietary changes [11]. Survey respondents were selected from the National Psoriasis Foundation (U.S.) email distribution list and were 50.4 years old on average, 73% female and had variable disease severity [11]. Criteria which include: usage of a tomato-based sauce (sofrito) 2 or more times per week and incorporation of shellfish into the diet are at odds with reported positive skin responses following removal of shellfish and nightshades (e.g. tomato) [11]. Care must also be taken when interpreting the effect of alcohol consumption on psoriasis presentation. Whereas the PREDIMED questionnaire favourably awards points for consumption of 7 or more glasses of wine per week [143], alcohol has also been named as one of the main dietary triggers capable of aggravating psoriasis severity [11]. Interestingly, the survey study (n = 481) also found that of the 5.8% of respondents that had trialled a Mediterranean diet, 48.4% of them reported subsequent symptomatic improvement [11]. A major limitation to the study would be the absence of defined criteria for the constitution of a Mediterranean diet amongst respondents, as used by Barrea et al. [11].

Table 2 [19,40,121,140−142,144−147], presents a culmination of the relevant clinical trials involving both diet and psoriasis. It reveals that significant improvement to psoriasis severity resulted from low energy diets; increased Omega 3/oily fish (in some instances) and dietary intervention. Concurrent alternative treatment use is noted where applicable. Improvement following Omega 3 administration represents one of the clearest indications that diet is correlated with psoriasis. As discussed, it is most likely due to the production and inhibitive competition for the same enzymes of anti-inflammatory eicosanoids [25]; the suppressive effect on antigen presenting cells [19] and a decreasing Omega 6 to Omega 3 ratio [13]. Despite not being the focus of this review, weight loss should be considered as a useful adjunct to dietary change recommendations, particularly given the association between BMI and psoriasis [12,38,39,41] and the recent findings by Klingberg et al. (see Table 2). There are a number of possible mechanisms through which psoriasis improvement could be achieved following weight loss: a decrease in white adipose tissue may lead to a reduced inflammatory profile; very low energy diets, used to achieve significant weight loss with <800 kcal per day, allow the body to use up alternate sources of energy (such as ketone bodies) and thus attenuate the effect of T cells which rely on aerobic glycolysis; it increases the levels of adiponectin and corticosteroids [39] and,

fasting and loss of body weight leads to IL-4 production [148] which, as mentioned previously, promotes IL-10 release [53] and thereby halts the action of TNF-α [129].

2.2.6. Dietary intervention: bile acids and potential solutions to SIBO

The production and digestive function of bile salts are already well established [59], however their involvement in the innate immune system through receptor activation is a more recent discovery [149]. Farnesoid X Receptor (FXR) is activated by increased intracellular bile acid levels and suppresses inflammatory mediators like NF-$\kappa\beta$ [59]. Mice deficient in this receptor demonstrated signs of hyperlipidaemia such as elevated plasma triglycerides, low density lipoprotein (LDL) cholesterol and free fatty acids [149]. As previously mentioned, studies comparing psoriatic patients to controls have revealed increased levels of total cholesterol, LDL cholesterol and/or triglycerides [2]. The production of oxidised LDL is positively associated with increased ROS levels and has been observed to aggregate in psoriatic lesions, particularly in more severe cases [2]. Oxidised LDL can also induce an immune response which leads to the generation of autoantibodies in psoriatic patients [2]. Administration of bile salts to diabetic and obese mice led to decreased LDL, triglycerides and fatty acids facilitated by increased hepatic clearance and mediated by FXR activation [149].

A 2003 study by Gyurcsovics and Bertók [63] may provide a further link between diet and psoriasis. They had previously realised that many of the symptoms observed in psoriasis, e.g. increased lysosomal enzymes and altered lipid metabolism, were also present in endotoxaemia. Gyurcsovics and Bertók theorised that LPS was responsible for the resultant cytokine release and psoriasis pathogenesis, following translocation in the bloodstream. Furthermore, they suggested that increased LPS in the bloodstream were connected to bile acid deficiency. For the study, which was unblended and not randomised, patients were divided into those receiving bile acid supplementation (n = 551) and those receiving conventional treatment (unspecified; n = 249). Of those receiving conventional treatment, 6% remained asymptomatic after 2 years (P < 0.05). 57.9% of those in the supplement group were asymptomatic after 2 years. The results from study are, without doubt, impressive. However, there were a number of caveats with their study. Patients were allowed to continue with other treatments such as antibiotics and anti-histamines. No record of patient numbers using alternate therapies was documented in the study. Finally, 73 patients did not return for a check-up following symptom improvement. This method of treatment would greatly benefit from further investigation with a well-designed rigorous clinical trial.

Antibiotics are a common treatment for SIBO [150] and may therefore be a potential short-term treatment for psoriatics. However, as they are used to reduce the overall bacterial load and thereby reduce both pathogenic and commensal bacteria, they compromise the myriad of microflora benefits and may cultivate an environment for the development of chronic disease. A rise in pathogenic bacteria, caused by disruption to gut microflora, can also result in increased neutrophil and macrophage infiltration [151]. Germ free rats produce less bile acids [59] indicating the essential role of a healthy microbiota in digestion. Flavanoids, which can suppress keratinocyte and mast cell activation and IL-1β and TNF-α [152], require a healthy microbiota for both flavonoid conversion and utilisation [153]. This would suggest that long term usage of antibiotics for treatment of psoriasis is inadvisable.

An alternate way to control SIBO may revolve around diet such as fructose restriction or a Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAPs) diet. This reduces fermentable foodstuffs in the diet, alleviating gas

Table 2
Review of *Pubmed* results for "Diet AND Psoriasis". Only clinical trials were selected. The Boolean "AND" was used to narrow the search to articles relating to both psoriasis and diet. Irrelevant studies, pertaining mostly to the benefits of drug treatment, in a language other than English or repeats were excluded from the review. One study was unavailable and another relating to fumaric acid treatment was excluded due to the large number of side effects associated with treatment. Some studies lacking in an effective control were included, for sake of completeness, although this has been noted in the study design.

Study	Study Design	Measure of Psoriasis Severity	Intervention	Results
Klingberg et al., 2019 [39]	Clinical Trial. No control, unblinded. 6 months. N = 41 (63% women) BMI ≥ 33	Minimal Disease Activity (MDA), CRP, Body Surface Area, Disease Activity in Psoriatic Arthritis (DAPSA)	BMI < 40 = 12 weeks very low energy diet (VLED) of 640 kcal. BMI >40 = 16 weeks VLED. Food was then reintroduced over 12 weeks. Further follow up will occur 2 years post baseline.	Median weight loss at 6 months post baseline was 18.7 kg. Median BMI decreased from 35.2 to 29.7. Median CRP decreased from 4 mg/L to 2 mg/L (P < 0.041). Median Body Surface Area decreased from 1.6% to .9% (P < 0.014). MDA decreased from 29.3% at baseline to 53.7% at 6 months. Baseline correlation found between CRP and DAPSA with BMI. 12% of patients had a flare to psoriatic lesions at 3 months. Consistent drug treatment from 3 months before to 6 months post baseline.
Naldi et al., 2014 [121]	Randomised controlled trial, assessor blind. 20 weeks. N = 303 (215 men & 88 women) BMI ≥ 25	PASI > 10	To promote dietary and lifestyle changes following 4 weeks of ineffective treatment. 2 study arms composed of either a complete diet and exercise plan (intervention) or informative counselling.	Study focused mostly on weight loss and low intensity exercise. Drug treatment was allowed for duration. The intervention was more efficient at decreasing severity of psoriasis.
Jensen et al., 2013 [144]	Randomised clinical study, controlled. 16 weeks. N = 60 BMI = 27-40	PASI and Dermatology quality of life index	To assess the effect of weight reduction on psoriasis severity. Participants were divided into an intervention group following a low energy diet (800−1000 kcal/day) for 8 weeks and approx. 1200 kcal/day for a further 8 weeks or a control group.	Intervention Group: Greater improvement vs control (P < 0.001) with a corresponding higher reduction in psoriasis severity according to Dermatology quality of life index (P < 0.02). PASI improvement did not achieve statistical significance.
Del Giglio et al., 2012 [40]	Randomised controlled study, investigator blind. Part II of study: 24 weeks and a 12 week follow up N = 42. BMI ≥30 Cases of psoriatic arthritis excluded	PASI	Patients assigned to one of two groups: an intervention group which received a low energy diet as determined by a dietitian (1200−1600 kcal/day) or a second control group which received no dietary recommendations.	Intervention Group: Highly significant weight loss and BMI reduction which was maintained up to week 24, compared to the control group. Both Groups: previously on methotrexate for their psoriasis and experienced PASI improvement, seemingly unrelated to diet (no data shown).
Soyland et al., 1994 [145]	Double blind. No 'true' control. Randomised, multicentre trial. 4 months. 19 patients with psoriasis and 21 with atopic dermatitis	PASI used for psoriasis participants	Participants randomly assigned into an Omega 3 fatty acid group or a corn oil 'control' group. Both groups also received α-tocopherol.	Omega 3 Group: Eicosapentaenoic acid and docosahexaenoic acid increased significantly CD25 lymphocytes decreased, P < 0.05. Corn Oil Group: No significance was observed in the serum phospholipids however TNF-α did increase, P < 0.01.
Soyland et al., 1994 [19]	Double blind, randomised, multicentre trial. No 'true' control group. 4 months during winter N = 145 (124 completed the trial). Psoriasis involving >8% body surface	PASI evaluated by physicians	Patients were assigned to either the fish oil group: 6 × 1 g capsules of Omega 3 rich fatty acids per day (51% eicosapentaenoic acid and 32% docosahexaenoic acid) or to the corn oil group: 6 × 1 g capsules or Omega 6 rich fatty acids per day (26% oleic acid and 56% linoleic acid). Both contained 3.6 International Units of α-tocopherol. Both groups were asked to lower saturated fat intake and provided with written information. Fat intake was estimated before and after the study by a nutritionist using 48-h patient recall.	Fish Oil: Very long chain Omega 3 fatty acids significantly increased in serum phospholipids, particularly eicosapentaenoic acid. Docosahexaenoic acid and docosapentaenoic acid increased by 39% and 70% respectively. Conversely, oleic acid, γ-linolenic acid and linoleic acid decreased in serum phospholipids. The ratio of arachidonic acid to eicosapentaenoic acid changed from 5 to 1.1 and the Omega 6 to Omega 3 ratio changed from 3.8 to 1.5. Fasting serum triacylglycerol decreased by

Table 2 (*continued*)

Study	Study Design	Measure of Psoriasis Severity	Intervention	Results
				25%, P < 0.05. Corn Oil: Increase in docosahexaenoic acid and polyunsaturated to saturated fat ratio increased (P < 0.01). Examination of clinical variables found no overall difference between the groups.
Grimminger et al., 1993 [146]	Double blind Randomised, placebo controlled 10-day trial N = 20	PASI≥10 (range 10–90%)	Participants received an infusion of either Omega 3 or Omega 6 rich fatty acid lipid emulsion.	Omega 6 Group: Moderate improvement (16–25% from baseline) by day 10. Neutrophil platelet activating factor was increased in the Omega 6 group but not the Omega 3 group. Omega 3 Group: Marked improvement by day 10 (45 –76%), P < 0.05. There was also a 10-fold increase in lipoxygenase not observed in the Omega 6 group.
Collier et al., 1993 [141]	Randomised clinical trial No control 16 weeks N = 18	Details not provided	All patients were advised to eat 170 g white fish daily for 4 weeks. Patients were then randomised to continue consuming white fish or oily fish for a further 6 weeks.	Oily fish was found to demonstrate a modest improvement in psoriatic severity, P < 0.01. No details of compliance or other dietary protocols provided.
Lassus et al., 1990 [142]	Clinical trial, No Randomisation No control/placebo 8 weeks. N = 80 (34 also had psoriatic arthritis)	PASI Mean = 3.56	Patients were treated with 1122 mg/day eicosapentaenoic acid and 756 mg/day docosahexaenoic acid.	Complete regression of disease observed in 7 patients, 13 experienced improvements of at least 75%, 14 experienced little benefit. Patients with psoriatic arthritis reported lessened joint pain.
Bittiner et al., 1988 [140]	Clinical trial Double blind, Placebo controlled 8 weeks. N = 28	Not provided "Chronic stable"	Patients allocated to receive either 10 fish oil capsules or 10 placebo olive oil capsules daily.	Fish Oil Group: less itching, reddening and scaling. Placebo Group: No improvement.
Bjorneboe et al., 1988 [147]	Double blind Block randomised Clinical trial 8 weeks. N = 37	Not provided "Stable psoriasis vulgaris"	Participants were split into a treatment group consuming 10 fish oil capsules or 10 placebo capsules of olive oil daily.	No significant clinical improvement observed in either group after 8 weeks. Fish Oil Group: significantly elevated levels of Omega 3 serum phospholipids and decreased Omega 6 levels.

Abbreviations: PASI, psoriasis area and severity index; CD, cluster of differentiation; TNF, tumour necrosis factor; CRP: C-Reactive Protein; MDA: Minimal Disease Activity; DAPSA: Disease Activity in Psoriatic Arthritis.

production in the gut [150]. Also, prebiotic and probiotic usage allow the development of a ratio favourable to commensal bacteria [150] and result in decreased LPS production. Inclusion of non-enzymatic antioxidants in the diet such as vitamin C and vitamin E are important for the prevention of lipid peroxidation [2] and to reduce the damaging effects of oxidative stress by increasing total

Table 3
Beneficial foods which may confer an advantage in psoriatics. Studies include secondary and primary literature.

Nutrient/Food	Study	Benefit
Prebiotics: chicory root, dandelion greens, artichoke, onion, garlic, leeks, asparagus	Review: McCusker & Sidbury, 2016 [155]	Promote the growth of commensal bacteria; assists the cultivation of a probiotic effect
Zinc: Oysters, Chickpeas	Case-control study: Sheikh et al., 2015 [154]	Increases superoxide dismutase, the enzyme involved in breaking down reactive oxygen species
Vitamin D3	Review: McCusker & Sidbury, 2016 [155]; Review: Barrea et al., 2017 [42]	Improves general health and facilitates improvement to PASI score
Antioxidants (Vitamin E, Selenium and Coenzyme Q10)	Review: McCusker & Sidbury, 2016 [155]; Review: Wolters, 2005 [29]; Review: Spiteller, 2010 [21]	Lowered inflammation, PASI severity and oxidative stress. Reduced psoriasis risk
Carotenoids: carrots, apricots, kale	Review: Pappas et al., 2016 [156]	Elimination of free radicals; photoprotection; decreases lipid peroxidation. Note: consumption with protein decreases absorption, whereas consumption with fat increases absorption
Flavanoids	Review: Spiteller, 2010 [21]	Subclass of polyphenols: free radical scavengers
Alkamides, e.g. *Echinacea purpurea*	Review: Manayi et al., 2015 [157]	Inhibitory effect of TNF-α and inflammatory enzymes and cytokines
Curcumin/Turmeric	Controlled Murine-Model: Zhang et al., 2016 [158]	Inhibition of inflammatory pathways and cytokines
Low leucine diet	Controlled Murine-Model: Witham et al., 2013 [159]	Decreases antiapoptotic protein

Abbreviations: PASI, psoriasis area and severity index; TNF, tumour necrosis factor.

antioxidant capacity [20]. A reduction in total antioxidants has been observed in psoriatics [2] and a significant zinc deficiency was also noted in psoriatics *vs.* controls ($P < 0.0001$) [154], with an uneven distribution observed between unaffected and lesioned skin. Supplementation of zinc or increasing consumption of antioxidant-rich foods could prove useful when treating psoriasis. To date, however, these methods have not been verified in studies to improve psoriasis but may have potential for further research. Table 3 [21,29,154—159] provides a list of foods/nutrients which could provide benefit to psoriasis and associated co-morbidities. Important to note, however, is that a FODMAPs diet would seek to lower the number of prebiotics e.g. onion and garlic, in the diet.

3. Conclusion

Psoriasis, as an affliction, is complex. Significant improvement to psoriasis severity was found to result from low energy diets; increased Omega 3/oily fish (in some instances); intensive exercise and dietary intervention. The data clearly suggest that patient benefit could arise through the expertise of dietitians, exercise coaches and therapists, as well as the more traditional dermatologist role. Further study is required, specifically examining the connection between the localised HPA axis in the skin; dysbiosis, LPS and bile acid deconjugation; the potential efficacy of boosting Vitamin D-rich foods and/or supplementation in the diet and investigation into the role of sedentary lifestyles in psoriasis presentation. Additionally, the next steps should include creation of a psoriasis-specific lifestyle plan and further elucidation of the importance of these lifestyle changes to health-care providers. Studies should also aim to utilise one scoring system to achieve uniformity. PASI seems to be the most accurate and well known. Another common obstacle to understanding psoriasis is the lack of clarification around dietary fat in studies. Often when examining the consequences of consumption of a high-fat diet, for example, the fat-type is not documented. Definite risk-factors and treatments must be deduced from further, well-conducted clinical trials. In the meantime, promotion of a lowered Omega 6: Omega 3 fatty acid ratio, frequent exercise and the ingestion of probiotic and prebiotic foods may prove useful and accessible to those suffering with psoriasis.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.05.006.

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