DOI: 10.1111/jdv.16614 JEADV

SUPPLEMENT ARTICLE

# Clinical and biological impact of the exposome on the skin

T. Passeron[1,2,*] J. Krutmann,[3,4] M.L. Andersen,[5] R. Katta[6] C.C. Zouboulis[7]

[1]Côte d'Azur University, Department of Dermatology, University Hospital Centre Nice, Nice, France
[2]Côte d'Azur University, INSERM U1065, C3M, Nice, France
[3]IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany
[4]Medical faculty, Heinrich-Heine-University, Düsseldorf, Germany
[5]Department of Psychobiology, Universidade Federal de São Paulo (UNIFESP)/Escola Paulista de Medicina, São Paulo, Brazil
[6]Volunteer Clinical Faculty, Baylor College of Medicine, McGovern Medical School at UT Health, Houston, TX, USA
[7]Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane, Dessau, Germany
*Correspondence: E-mail: thierry.passeron@unice.fr

**Abstract** The skin exposome is defined as the totality of environmental exposures over the life course that can induce or modify various skin conditions. Here, we review the impact on the skin of solar exposure, air pollution, hormones, nutrition and psychological factors. Photoageing, photocarcinogenesis and pigmentary changes are well-established consequences of chronic exposure of the skin to solar radiation. Exposure to traffic-related air pollution contributes to skin ageing. Particulate matter and nitrogen dioxide cause skin pigmentation/lentigines, while ozone causes wrinkles and has an impact on atopic eczema. Human skin is a major target of hormones, and they exhibit a wide range of biological activities on the skin. Hormones decline with advancing age influencing skin ageing. Nutrition has an impact on numerous biochemical processes, including oxidation, inflammation and glycation, which may result in clinical effects, including modification of the course of skin ageing and photoageing. Stress and lack of sleep are known to contribute to a pro-inflammatory state, which, in turn, affects the integrity of extracellular matrix proteins, in particular collagen. Hormone dysregulation, malnutrition and stress may contribute to inflammatory skin disorders, such as atopic dermatitis, psoriasis, acne and rosacea.
Received: 6 April 2020; Accepted: 5 May 2020

All authors contributed equally.

## Conflict of interest

The publication of this supplement has been supported by Vichy Laboratories (L'Oréal). All authors have served as Advisory Board members for Vichy Laboratories (L'Oréal).

## Funding sources

None.

## Section 1. Clinical and biological impact of solar radiation on the skin

### Key points

- Photoageing, photocarcinogenesis and pigmentary disorders are well-established consequences of chronic exposure of the skin to solar radiation.
- Various skin conditions are induced or modified by solar exposure, and the impact may be negative or beneficial.
- Improvement of several skin conditions, such as psoriasis, atopic dermatitis, vitiligo and localized scleroderma, can be obtained from solar or artificial ultraviolet radiation (UVR) exposure, although photosensitive forms do exist.
- Genetic background and the efficiency of the DNA repair machinery have a marked impact on skin sensitivity to the acute and chronic effects of solar radiation.

### The solar spectrum

The solar spectrum is composed of various wavelengths (Fig. 1). Longer wavelengths penetrate deeper into the skin than shorter rays with each wavelength having both different and overlapping effects. About 2–5% of solar radiation is ultraviolet (UV), 47% is visible light (VL), and 51% is infrared light (IR). Short wavelength radiations in the UV range have higher energy and have been shown to be responsible for the majority of known photobiological effects of the sun on the skin. UVB (315–280 nm) mostly affects the epidermis and can only penetrate to the

papillary dermis. Similarly, short-wave UVA (UVA2, 340–315 nm) also mostly affects the epidermis, whereas long-wave UVA (UVA1, 400–340 nm) penetrates deeply into the dermis.

Photoageing, photocarcinogenesis, photoimmunosuppression, photodermatoses and pigmentary disorders are well-documented consequences of chronic exposure of the skin to solar radiation.[1]

### Solar radiation and skin cancers

Ultraviolet light is an established carcinogen that is responsible for more than 50% of all human malignancies. Of the three major types of skin cancer, basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) rarely metastasize, whereas primary cutaneous malignant melanoma (MM) is often characterized by aggressive metastatic growth and poor prognosis. UVR causes nearly 65% of MM and 90% of keratinocyte carcinomas.[1] There is good evidence that both UVB and UVA promote melanoma development.[2] However, the potential role of VL and IRA in skin cancer is unknown.

### Photoageing

Sun-exposed skin (e.g. face and neck skin) has a prematurely aged appearance compared to sun-protected areas (e.g. the trunk, thigh or underarm) and is characterized by various clinical features, including wrinkles, dullness, pigmentary changes, laxity, roughness and telangiectasia. Exposure to solar radiation causes cells to produce reactive oxygen species (ROS), which are the primary cause of skin damage and photoageing (see recent reviews[3,4]). The epidermis of UV-exposed skin produces several enzymes such as matrix metalloproteinases (MMPs), urokinase, plasmin and heparanase, which degrade dermal collagen fibres and elastic fibres in the dermis, and components of epidermal basement membrane.[5]

In addition to UV radiations, IRA and VL also promote skin ageing due to the formation of radical species. VL and heat of natural sunlight (IR) play a role in modulating the expression of MMPs and procollagen, and inflammatory cell infiltration in human skin.[6] IRA radiation was shown to induce MMP-1 upregulation, which was reduced by applying a sunscreen supplemented with an antioxidant cocktail, whereas sunscreen alone did not provide significant protection against IRA.[7] A recent *in vivo* pilot study has shown that all spectral regions (UV, visible and near IR) cause free radical formation and hence could promote premature skin ageing, even in darker skin types.[8]

### Impact of genetic background on sensitivity to solar radiations

There is interindividual variation to the acute and chronic effects of UVR exposure, and genetic background plays an important role in skin sensitivity, which depends on phototype and constitutive pigmentation. Although the most obvious difference between dark and fair skins is the quantity of melanin, the distribution of melanins that better protect the DNA of the keratinocyte stem cells located in the basal layers of the epidermis in dark skin individuals is even more important.[9] The photoprotective effect of eumelanins mostly found in black skin, compared to the pheomelanins of white skin that produce radical species after UVR is critical in terms of photoprotection. Finally, the difference between dark and light skin in their ability to repair the DNA after exposure to UV radiation also helps explain the different susceptibilities to UVR.[10]

### Pigmentation and pigmentary disorders

More than 170 genes are involved in pigmentation regulation in humans, and solar exposure plays a key role. Both UVB and UVA contribute to acquired skin pigmentation (also called tanning). Although UVR (mostly UVB) can directly stimulate melanocytes, most of the impact of UVR on melanogenesis is mediated by epidermal keratinocytes.[11] It has now been demonstrated that long-wave UVA (UVA1) exposure induces skin darkening to a similar extent in skin phototypes III to VI and the pigmentation is associated with cellular changes in all skin phototypes, including darker skin.[12]

Shorter wavelengths of VL have a propigmenting role in skin types III and higher.[13] Red light has no or weak effect on pigmentation, but blue-violet light is propigmenting at doses corresponding to 'physiological' exposures (1h30 during summer).[14] The shorter wavelengths of VL [blue-violet light, high energy

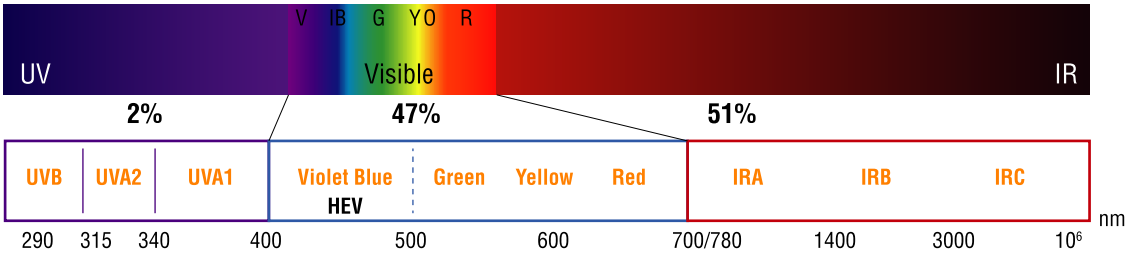



**Figure 1** The solar spectrum.

visible (HEV)] have recently been shown to induce a hyperpigmentation through a specific blue light photoreceptor in melanocytes called opsin 3, which activates sustainably the melanogenesis pathway.[15]

The very low irradiance of blue light from screens would not induce pigmentation.[16] At 30 cm from a powerful TV screen, the irradiance of blue light was measured as 30 μW/cm$^2$, whereas solar intensity at the ground level is approximatively 1000 W/m$^2$ and the irradiance of the blue part accounts for approximatively 6 mW/cm$^2$, i.e. 200 times higher than for a digital screen. At least 150 h of exposure to digital screens would be required to achieve the minimal pigmentary dose. The irradiance of the light has a profound impact on its biological effects, and the duration for achieving the dose capable of inducing pigmentation is significantly longer with devices than with sun exposure. Thus, a recent study demonstrated that short-term exposure to blue light emitted by electronic devices does not worsen melasma.[17]

Melasma is a common hyperpigmentary disorder previously considered to be the main consequence of female hormone stimulation on a predisposed genetic background. However, there is increasing evidence that melasma is a photoageing skin disorder.[18] Thus, altered basal membrane, activation of keratinocytes, but also elastosis, and increased vascularization in the dermis of lesional skin induce the secretion of propigmenting factors by fibroblasts and endothelial cells that stimulate melanocytes.

Broad-spectrum sunscreens against UVB, UVA and HEV offer better protection against melasma relapses since most patients have a worsening of their melasma lesions even when using effective UVB and UVA protection during the summer.[19] Similarly, combined protection to protect against VL is important for cutaneous hyperchromias (sun spots) on the face.[20] Recently, ambient light was shown to be sufficient to promote postinflammatory hyperpigmentation.[21] Finally, UVA1 plus HEV irradiation induces a greater hyperpigmentation in skin phototypes IV–VI compared to pure HEV.[22] As these data show that solar radiations from UVB to HEV impact acquired hyperpigmentation and pigmentary disorders, combined protection against UVB, UVA and HEV is required for individuals of Fitzpatrick phototype ≥III to delay sun-induced pigmentation and for individuals of Fitzpatrick phototypes I–VI with pigmentary disorders (PIH, melasma, actinic facial lentigo).

## Impact of solar radiation on dermatoses

Solar radiation can trigger or worsen several dermatoses (called photodermatoses) that will not be covered in this review, but instead we will focus on the impact of solar radiation on some of the most common skin disorders.

*Acne* Ultraviolet radiation has a demonstrated anti-inflammatory role in acne. Blue light has anti-inflammatory effects on keratinocytes by decreasing the cytokine-induced production of IL-1α and ICAM-1. In addition, blue light demonstrated synergistic effects with low-dose UVB light.[23] Blue light can also be beneficial as it has a phototoxic effect on the haem metabolism of *Cutibacterium acnes*. However, UV can worsen the presence of retentional lesions resulting from hyperkeratinization of the pilosebaceous canal by modifying lipids and thickening the stratum corneum (SC). Two studies in India ($n$ = 309 and $n$ = 402 subjects) reported worsening of acne in summer in 23% and 56% of patients, respectively, due to the sun exposure, heat, marked humidity and sweating.[24,25]

*Rosacea* Rosacea is a chronic inflammatory disease, with a genetic component, that has been shown to be particularly common among fair-skinned people of northern European or Celtic origin. UV light is a well-known trigger causing worsening of rosacea and, therefore, the daily use of sunscreens is recommended.[26] UVR stimulates the production of LL-37 and induces oxidative stress in the skin. Furthermore, UV radiation stimulates angiogenesis, which promotes telangiectasia. The pivotal role of sunlight is supported by the distribution of erythema and telangiectasia on the facial convexities. Sun-protected areas, such as the supraorbital and submental areas, are typically spared. However, epidemiologic studies demonstrate that only 17–31% of rosacea patients report worsening of symptoms by sunlight, and several photo-provocation studies in rosacea patients have failed to show heightened skin sensitivity to the acute effects of UV radiation.

*Psoriasis* Sun exposure usually improves psoriasis lesions, and heliotherapy has been used to reduce the extent and severity of psoriasis since antiquity. However, worsening of psoriasis after sun exposure occurs in 5–10% of patients and is more frequently observed on the hands and forearms, in individuals with skin type I, older patients, and patients with a personal history of polymorphic light eruption or familial history of photodermatoses. Furthermore, there is a risk of Koebner phenomenon following sunburn.[27]

*Atopic dermatitis* Sun exposure usually improves atopic dermatitis (AD) lesions but photosensitive AD exists and seems to be more frequent in women than in men. Photosensitive AD is characterized clinically by a photo-distributed rash in patients who fulfil the criteria for AD. In a retrospective analysis of 17 patients with long-standing AD who suddenly developed photosensitivity to UVA, the onset of photosensitivity was reported during spring and summer and during exposure to artificial UVR as part of the patients' treatment regimen.[28]

## Beneficial effects of solar radiation

Although the most well-known positive effect of solar radiation is the UVB-induced production of vitamin D in skin, solar

radiations provide many other benefits. Tanning is often considered to be cosmetically desirable, and photoadaptation after exposure to UVR may give some measure of protection by reducing the risk of sunburn, with the caveat that photoadaptation does not necessarily protect against DNA damage and the development of skin cancer.[29]

The improvement of several skin conditions, such as psoriasis, AD, vitiligo, mycosis fungoides or localized scleroderma, can be obtained from solar or artificial UVR exposure.[30] Blue light is also very useful for treating seasonal depression. In mice, β-endorphin is synthesized in skin after exposure to UV resulting in elevated plasma levels that contribute to well-being, pain relief and relaxation.[31]

Skin contains significant stores of nitrogen oxides, which can be converted to nitric oxide (NO) by UVA radiation and exported to the systemic circulation causing arterial vasodilatation and reduced blood pressure.[32] In response to UVA and UVB radiation, normal human keratinocytes secrete NO, which stimulates pigmentation.[33] Furthermore, UVA-induced NO may also play an antimicrobial role and act as a neurotransmitter.[34] Upon UV exposure, sensory nerves in the skin release neuropeptides, such as substance P, which is important for vasodilation and healing. Exposure of healthy skin to UVR directly upregulates antimicrobial peptides that may serve to protect the skin from risks due to biophysical barrier compromise and immunosuppression caused by UVR exposure.[35] Additionally, melatonin, among other compounds, has a regulatory effect on circadian clock genes, which may help ensure the homeostasis of stem cells.[36]

Deleterious and beneficial effects of solar radiation on the skin are summarized in Table 1.

### Conclusions

Solar radiation and skin have interplayed for thousands of years and shaped the great variety of skin colours in humans. In addition to the visible consequences, the results of this genetic evolution strongly affect the response of the skin to the numerous positive and negative impacts of solar radiation. Due to the knowledge acquired over recent decades, we can now propose adapted behaviours and sunscreens depending on skin type, living location and habits, as well as potential skin disorders, in order to benefit from the positive effects of the sun while being protected from its harmful consequences.

## Section 2. Clinical and biological impact of air pollution on the skin

### Key points

- Exposure to traffic-related air pollution contributes to skin ageing based on epidemiological and mechanistic evidence.
- Exposure to traffic-related air pollution contributes to the pathogenesis of atopic eczema based on many epidemiological studies, but also on some mechanistic evidence.
- Air pollution may be linked to acne.
- Air pollution and UV radiation negatively interact with each other.

### Impact of air pollution on skin ageing and pigmentation

*Particulate matter and lentigines* The relationship between air pollution and skin ageing has recently been reviewed by Krutmann *et al.*[3] In brief, a relationship between air pollution and skin ageing was first shown in a cohort of elderly Caucasian women.[37] In this cross-sectional study, exposure to traffic-related air pollution, i.e. soot (such as diesel exhaust particles; DEP) and fine particulate matter ($PM_{2.5}$), was found to be significantly associated with lentigines (pigment spots) on the face. These findings were later corroborated and extended in further epidemiological studies, many of which were conducted in China.[38–45]

One of these studies showed that indoor air pollution, specifically from heating and cooking with fossil fuels in rural areas of China, was significantly associated with an increased risk of 5–8% for severe facial wrinkles and of 74% for fine wrinkles on the back of the hands, independent of age and other influences on skin ageing.[41] The combustion of coal and biomass indoors emits a substantial amount of toxic pollutants including particulate matter (PM), polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, nitrogen oxides ($NO_x$) and sulphur dioxide ($SO_2$).

To assess the impact of long-term exposure to chronic outdoor urban pollution on signs of facial ageing, two cohorts of Chinese women ($n$ = 204) of comparable ages living in a highly polluted (Baoding) or less polluted city (Dalian) were analysed by expert visual grading of wrinkles and skin texture, pigmentation disorders, and skin pores/skin redness, as well as referential photographic Atlas.[45] The increased severity of almost all facial signs was mostly observed in the older group (40–45 years) of women living in Baoding. Traffic-related air pollution and long-term chronic exposure to pollution for at least 15 years were found to be correlated to an increase in pigmentary disorders (spread macules, simplex lentigines).[40,45]

The precise mechanism through which PM/soot causes skin ageing and, in particular, the formation of pigment spots, has not yet been fully elucidated. In mechanistic studies with standardized mixtures of DEP to simulate traffic-related soot, topical application of DEP *ex vivo* onto the surface of human skin models or *in vivo* onto the surface of healthy human skin caused an oxidative stress response. Although not fully understood, it appears that the oxidative stress response stimulates increased synthesis of melanin and ultimately skin pigmentation via the p53 signalling pathway.[46] Therefore, DEP might induce skin pigmentation via a stress response, which was previously described for UVB-induced skin pigmentation. This is consistent with preventive studies showing that application of topical antioxidants

**Table 1** Deleterious and beneficial effects of solar radiation on the skin

| | Action | Effect on health | References |
|---|---|---|---|
| ***Deleterious*** | | | |
| Ultraviolet radiation exposure (VL? IRA?) | Photocarcinogenesis | Skin cancer, e.g. basal cell carcinoma, squamous cell carcinoma, melanoma | 1,2 |
| Ultraviolet radiation exposure, VL, IRA | Photoageing. Production of reactive oxygen species, decrease of collagen production, increased metalloproteinases | Wrinkles, skin dullness | 1,2,5–8 |
| UVB, UVA, blue light | Melanogenesis | Pigmentary disorders, e.g. melasma, postinflammatory hyperpigmentation, actinic lentigos | 1,2,11–14,18–22 |
| Ultraviolet radiation exposure | Functional alteration and apoptosis of Langerhans cells and lymphocytes | Photoimmunosuppression, viral reactivation | |
| Ultraviolet radiation exposure, VL | Promotes inflammation and oxidative stress | Photodermatoses, e.g. polymorphous light eruption, chronic actinic dermatitis and solar urticaria | |
| Ultraviolet radiation exposure | Hyperkeratinization of the pilosebaceous canal | Worsening retentional acne lesions | |
| Ultraviolet radiation exposure | Oxidative stress and vasodilation | Rosacea triggers | 26 |
| Ultraviolet radiation exposure | Photosensitivity | Worsening of some psoriasis and atopic dermatitis | 28 |
| ***Beneficial*** | | | |
| UVB | Mediates natural synthesis of vitamin D | Multiple health benefits, especially healthy bones | 1 |
| Ultraviolet radiation exposure | Tanning and photoadaptation | Cosmetically desirable, some protection against sunburn | 29 |
| Blue light | Mediates β-endorphin production | Seasonal depression, reduces stress, pain relief | 31 |
| UVR | Phototherapy | Improves, for example, psoriasis, atopic dermatitis, vitiligo, cutaneous lymphoma, localized scleroderma | 30 |
| UVA | Induces nitric oxide production | Lowers blood pressure | 32 |
| Ultraviolet radiation exposure | Nitric oxide production | Antimicrobial | 35 |
| UVA | Release of neuropeptides, e.g. substance P | Vasodilation and healing | 34 |
| Daylight | Inhibits melatonin production | Regulates sleep | 36 |

significantly reduced DEP-induced skin pigmentation *ex vivo* and *in vivo* in human skin.[46]

*Nitrogen oxide and ozone* In addition to PM/soot, nitrogen dioxide ($NO_2$) has been implicated to contribute to skin ageing and pigment spots. A significant association was detectable between exposure to $NO_2$ and facial pigment spots in both Caucasian and Han Chinese women.[40]

Reports from the SALIA population-based cohort study (806 women) showed exposure to increased ground-level ozone ($O_3$) was associated with wrinkle formation on the face.[47] This epidemiological observation seems reasonable in view of the large body of published mechanistic studies demonstrating that, as well as depleting antioxidants from the SC, ozone exposure elicits a signalling response that cascades down into the dermis resulting in elevated collagen-degrading MMPs (reviewed in Fuks *et al.*[47]). Five-year mean residential exposure to $O_3$ was modelled from two elderly German population-based cohort studies, the SALIA study and the BASE-II study, including a total of 2013 Caucasian men and women.[47] In contrast to $NO_2$ and PM/soot, epidemiological evidence demonstrated an adverse role of ozone in coarse wrinkle formation, but not with lentigines; these associations were independent of other known environmental risk factors, namely chronic UV exposure, and also of co-pollutants $PM_{10}$ and $NO_2$.[47]

Based on these epidemiological and mechanistic studies, it is now generally assumed that exposure to traffic-related air pollutants, including soot/ DEP, $PM_{2.5}$, $NO_2$ and ground-level $O_3$, causes skin ageing.

## Impact of air pollution on dermatoses

Indoor and outdoor air pollutants and aeroallergens play a key role in the aetiopathogenesis of the inflammatory response to allergens and in clinical manifestations of allergic respiratory and skin diseases, such as allergic rhinitis, asthma and AD.[48]

*Atopic dermatitis (eczema)* Although several epidemiological studies have assessed the association between air pollution and the epidemiology of AD, the data are inadequate for a meaningful meta-analysis.[49] Recently, a systematic review of 57 environmental epidemiological studies was performed to determine whether an association exists between air pollution (particles, $NO_x$, $SO_2$, $O_3$ or general traffic exhaust emissions) and AD.[50] A total of 23 out of 30 studies with small-scale exposure assessment found a significant positive association between AD and traffic exhaust-related emissions, especially from truck traffic.[50] Furthermore, there was a positive association between AD and air pollution induced by truck traffic, particularly when exposure was self-assessed in a small-scale analysis (five out of five studies), while a similar association was detected in only two out of 15 cross-sectional studies with a measured background assessment.[50] Air pollution and incidence of AD were investigated in recent birth cohort studies in East Asia, in which exposure to typical traffic exhaust air pollution during pregnancy led to increased rates of AD in the children.[50] In addition, an increase in symptom intensity of existing AD was observed with greater concentrations of particulate ($PM_{10}$, $PM_{2.5}$) and gaseous ($NO_2$, volatile organic compounds, $O_3$, $SO_2$) air pollutants in seven out of 10, predominately East Asian, studies.[50]

No evidence indicated that AD is impacted by 'large-scale' varying exposure to air pollutants such as $PM_{10}$ or $SO_2$, but numerous data suggest that 'small-scale' varying exposure to traffic exhaust pollution can influence the prevalence of AD. In addition, traffic exhaust emissions have been shown to impact the incidence (as assessed through maternal exposure during pregnancy) and the symptoms of AD.[50] Further research is required to identify which particulates contribute to these observed effects, and the potential mechanisms through which air pollution-induced health effects are mediated.

As air pollution-induced health effects require the penetration of pollutants into viable skin, skin barrier integrity is probably involved. In support of this, a recent study found that topical exposure of mouse skin to DEP increased the expression of the neurotrophic factor artemin in keratinocytes, through a mechanism involving the activation of AhR.[51] In addition, artemin induced the growth of nerve fibres (c-fibres) in the skin and caused pruritus.[51] These results suggest air pollutants penetrate through the skin and activate AhR in keratinocytes at the basal layer, leading to AD-like pathologies.

*Acne* In a time-series study in China over 2 years, high pollution levels of ambient $PM_{2.5}$, $PM_{10}$ and $NO_2$ were significantly associated with increased numbers of outpatient visits for acne vulgaris.[52] However, mechanistic evidence of the effect of pollution on acne is lacking.[53–55] A study comparing facial skin of subjects from Mexico City (exposed to pollution) with those from Cuernavaca (less exposed to pollution) demonstrated that polluted environmental conditions caused alteration in the sebum composition and increased the sebum excretion rate and SC damage;[43] disturbances of the SC and increased sebum are known to play a role in the pathology of acne.

### Interaction between air pollution and UV exposure

Solar lentigines, as the name suggests, are mainly caused by cumulative solar UV radiation. However, other environmental factors, such as traffic-related air pollution, may also contribute to their formation.[37,40] In urban environments, both UV radiation and air pollution are ubiquitous. Although exposure to either DEP or UV radiation, alone or in combination with other agents, has been identified as essential risk factors for skin ageing, there is a paucity of epidemiological evidence that UV radiation and high air pollution levels act additively.

An analysis of 799 Caucasian women in Germany revealed that facial lentigines are the consequence of an interplay between UV radiation and traffic-related air pollution.[56] In an urban environment, the UV index (based on the hour of day with maximal UVR intensity) was associated with more facial lentigines, whereas UVB from the whole daylight period was not associated with more facial lentigines because of its negative interaction with PM. In fact, a positive association between UVB from the whole daylight period and lentigines was only visible at low exposure levels of PM, while UVB exposure was associated with less facial pigment spots if PM levels were high.[56] This interaction was most likely due to a shielding effect of photochemical smog produced by UV radiation and $NO_2$.[57] Similarly, a negative interaction between UVB and traffic-related air pollution has recently been observed for the occurrence of BCC.[58]

Ultraviolet radiation may interact with air pollution either at the level of the troposphere or in skin.[59–61] However, although certain PAH environmental pollutants, e.g. benzopyrene, may be degraded by UVB, the resulting intermediates may also be toxic.[60] Hence, UVB can be beneficial for degrading toxic chemicals but in doing so it may lead to the production of other harmful compounds.

In human–hamster hybrid cells, the combination of UVA and DEP extracts induced significant cytotoxic and genotoxic damage through the photoactive production of singlet oxygen, which was not observed with either UVA or DEP extracts alone.[59] Furthermore, *in vitro* data have demonstrated that PAH and PM can aggravate UVA1-induced skin damage.[61]

## Conclusions

The dramatic global increases in the prevalence of allergic and other inflammatory diseases, such as AD, over recent decades have been widely attributed to industrialization and urbanization at the population level and quantifiable exposures, such as pollution, at the individual level. Consequently, air pollution is one of the best-studied exposome factors. Further research is now needed to explore the relationship between specific

environmental exposures to understand how they interact together to affect skin ageing and other skin conditions.

## Section 3. Clinical and biological impact of hormones on the skin

### Key points

- Human skin is a major target of hormones.
- Endocrine-disrupting chemicals induce skin disorders.
- Hormones decline with advancing age, influencing skin ageing.
- Hormone-associated exposome factors influence various dermatoses, including acne and rosacea.

### Human skin as a target of hormones

The human skin is a major target of hormones. Hormones affect its development and function through interaction with high-affinity receptors, such as several receptors for peptide hormones and neurotransmitters, steroid and thyroid hormones (Fig. 2). They exhibit a wide range of biological activities on the skin, with distinct effects caused by growth hormone/insulin-like growth factor 1 (IGF-1), neuropeptides, sex steroids, glucocorticoids, retinoids, vitamin D, peroxisome proliferator-activated receptor ligands, eicosanoids, melatonin and serotonin.[62] The pathways are regulated in most cases by different skin cell populations in a coordinated way indicating the endocrine autonomy of the skin. In addition to the classical hormones, certain vitamins exhibit properties of skin hormones.

### Endocrine-disrupting chemicals and human skin

Hormone-like effective compounds, e.g. hydrocarbons, aryl hydrocarbon receptor (AhR)-upregulating agents, compounds of plastics and dioxins, especially lipid-soluble compounds among them, are defined as endocrine-disrupting chemicals (EDCs). EDCs can be classified according to their origin, including natural and artificial hormones (e.g. phytoestrogens), drugs with hormonal side-effects, industrial and household chemicals, and side products of industrial and household processes. EDCs are exogenous and environmental compounds that have the ability to disrupt the production and actions of hormones through direct or indirect interaction with hormone receptors, thus acting as agonists or antagonists. They perturb the endocrine system and can

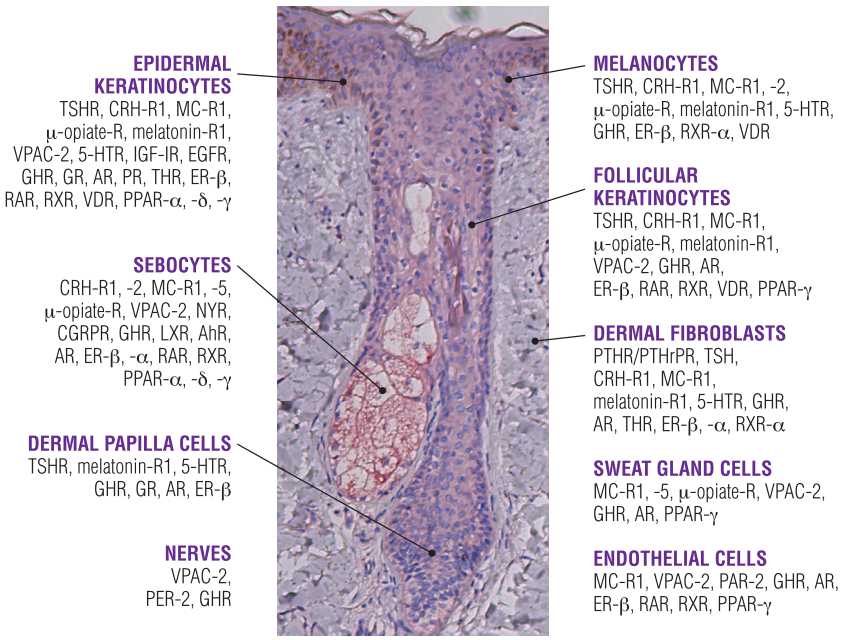



**Figure 2** Hormone receptors detected as being active in human skin cells. μ-opiate-R, μ-opiate receptors; 5-HTR, serotonin receptors (5-hydroxytryptamine receptors); AR, androgen receptor; CGRPR, calcitonin gene-related peptide receptor; CRH-R1, -R2, corticotropin-releasing hormone receptors types 1 and 2; ER-β, -α, oestrogen receptor types β and α; GHR, growth hormone receptor; GR, glucocorticoid receptor; IGF-IR, insulin/insulin-like growth factor I receptor; MC-R1,-R2, -R5, melanocortin receptor types 1, 2 and 5; melatonin-R1, melatonin receptor type 1; NYR, neuropeptide Y receptor; PAR, proteinase-activated receptors; PPAR-α, -δ and -γ, peroxisome proliferator activator receptors types α, δ and γ; PR, progesterone receptor; PTHR/PTHrPR, parathyroid hormone receptor/parathyroid hormone-related peptide receptor; RAR, retinoic acid receptors; RXR, retinoid X receptors; RXR-α, retinoid X receptor type α; THR, thyroid hormone receptors (isotypes a1 and b1); TSHR, thyroid-stimulating hormone receptor; VDR, vitamin D (calcitriol) receptor; VPAC-2, vasoactive intestinal polypeptide receptor type 2.

be carcinogenic, immunotoxic and hepatotoxic to human skin. In addition, their effects on certain skin cell populations may induce inflammatory and allergic skin diseases, chloracne, disorders of skin pigmentation, skin cancer and skin ageing.[63,64]

### Impact of hormones on the skin

The physiological decline in hormones occurring with age is one of the major factors that play a role in skin ageing. In addition, several age-associated diseases, such as diabetes, arterial hypertension and malignancies, are reflected by skin changes.[65]

*IGF-1* *In vitro* testing in sebocytes and fibroblasts demonstrated that IGF-1 is a key regulator of human skin ageing and declining IGF-1 levels with age may play a significant role in the reduction of skin surface lipids and thickness.[66] In a single-centre study with 21 healthy men over 60 years old with declining levels of serum IGF-1 (<350 U/L), the men treated with human growth hormone over 6 months experienced an 8.8% increase of muscle mass, 14.4% reduction of fat tissue, 1.6% enhancement of bone density and 7.1% increase of skin thickness.[67]

*Sexual hormones* Several functions of the human skin appear strongly dependent on biologically active sexual hormones, namely androgens, oestrogens and progestins.[68] Human skin is not only the target of androgens, but sebocytes can also synthesize androgens *in situ*.[69] Although human sebaceous glands can produce testosterone by *de novo* synthesis from abundant serum cholesterol, testosterone synthesized in cultured sebocytes is derived mainly via a shortcut pathway by using circulating dehydroepiandrosterone (DHEA).[70] DHEA has a weak androgenic effect but is a precursor hormone that is further metabolized into potent androgens and oestrogens.

Sexual hormones influence intrinsic skin ageing leading to cellular senescence, telomere shortening and decreased proliferative cell capacity, chronic inflammation, mitochondrial DNA single mutations and free radicals.[65]

*The menopause and andropause* Menopause is defined as permanent irreversible cessation of menses due to a decline in ovarian follicular activity and levels of 17β-oestradiol, progesterone and DHEA. The resulting deficiency in 17β-oestradiol in postmenopausal women decreases defence against oxidative stress and is associated with skin dryness (diminished skin moisture), atrophy (declining dermal collagen content leads to epidermal thinning), fine wrinkling (decreased skin elasticity), impaired wound healing, reduced vascularity and hot flashes.[71] In Korean women, the risk of facial wrinkling was found to increase significantly with more full-term pregnancies and with increased number of years since menopause.[72]

In menopausal skin, a negative change of the quantitative and qualitative sebum composition may affect the skin barrier function by decreasing photoprotection, antimicrobial activity and the delivery of fat-soluble antioxidants to the skin surface.[73]

Proteomic analysis has identified new biomarkers for postmenopausal skin.[74] Compared with the SC of young skin, the SC of postmenopausal skin has significantly increased levels of calmodulin-like skin protein, desmoglein 1, plakoglobin and heat shock protein 27, which might affect normal desquamation and explain the thicker SC in older skin. Conversely, transglutaminase 3, apolipoprotein D and acid ceramidase levels were significantly reduced in the SC of menopausal skin, probably reflecting the general reduction in sweat secretion leading to dry skin.[74]

Dermatoses after menopause may include atrophic vulvovaginitis, vulvar lichen sclerosus, dyaesthetic vulvodynia, hirsutism, alopecia, menopausal flushing, keratoderma climactericum and vulvovaginal candidiasis.

Decline of both testicular and adrenal function with ageing causes a decrease in androgen concentrations in men; DHEA levels start declining sharply over the age of 40, whereas testosterone levels decline slowly at a later age. Androgens affect sebaceous gland growth and differentiation, hair growth, epidermal barrier homeostasis and wound healing. Andropause is associated with thinning and hyperpigmentation of the skin.[75]

*Neurohormones* The hypothalamic–pituitary–adrenal (HPA) axis responds to physiological stress by secreting corticotrophin-releasing hormone (CRH), propiomelanocortin (POMC), α-melanocyte-stimulating hormone and adrenocorticotrophic hormone, as well as β-endorphin, mediating a release of glucocorticoids from the adrenal cortex. They are involved in thermoregulation, melanin synthesis, hair growth as well as in various immunological and inflammatory reactions in response to UV radiation and inflammatory stimuli.[76] Chronic stress, inflammation and disease with persistent stress-induced catecholamine and glucocorticoid excess may result in diminished keratinocyte and fibroblast function that underlies the ageing process of the skin.[77,78]

### Impact of hormones on dermatoses

Several acquired medical conditions have been associated with the sebaceous gland including acne vulgaris, seborrhoea, seborrhoea-acne-hirsutism-androgenetic alopecia syndrome, EDC-induced acne, rosacea, psoriasis, androgenetic or cicatricial alopecia, polycystic ovary, hyperandrogenism-insulin resistance-acanthosis nigricans syndrome, synovitis-acne-pustulosis-hyperostosis-osteitis, benign (sebaceous adenoma, sebaceoma) and malignant (sebaceous gland carcinoma) tumours.[79]

*Acne* Although factors contributing to the formation of acne include genetic predisposition, environmental factors also play a marked role, including diet-induced metabolic syndrome. It has been demonstrated that pi3k/Akt/FoxO1/mTOR signalling is

involved in the interplay between androgens, insulin, IGF-1 and a hyperglycaemic diet in acne. A rise in androgen levels can lead to acne due to elevated lipogenesis/sebum synthesis in sebocytes, changes in skin cell activity, inflammation and colonization of the hair follicles by *Propionibacterium acnes*.[80] Certain steroidogenic enzymes, such as 11β-hydroxysteroid dehydrogenase, are expressed in the sebaceous glands and upregulated in acne lesions. Hydrocortisone stimulates human sebocyte proliferation, and glucocorticoids attenuate sebum production.[81]

Genetic studies indicate that regulation of the androgen receptor is an important factor in severe acne. Further studies are required to understand the effect of abnormal oestrogen levels on the sebaceous gland and comedogenesis, considering changes observed in acne during pregnancy and around the time of menopause.[82]

In women, non-classic adrenal hyperplasia is associated with hyperandrogenic manifestations, such as severe acne refractory to treatment, hirsutism, androgenic alopecia or seborrhoea, as well as irregular menses and polycystic ovaries. Clinical determination of 17-hydroxyprogesterone, the immediate substrate for 21-hydroxylase, is used for biochemical diagnosis. Oral glucocorticoids and/or fludrocortisone reduce increased androgen production in non-classical adrenal hyperplasia. Its treatment is symptom-associated. Low-dose prednisolone (2.5–5 mg/day) or low-dose dexamethasone (0.25–0.75 mg) can be administered orally at bedtime.[83]

*Rosacea* Rosacea is a chronic inflammatory disease of the skin, whose pathophysiology has yet to be fully determined. Fluffy oedema, slight perivascular lymphocytic infiltrate and dilation of lymphatic vessels are clinical and histological characteristics compatible with rosacea. These signs start as an actinic lymphatic vasculopathy, and rosacea has been considered as a UV-induced dermatosis.[84]

On the other hand, hard facial oedema is common in rosacea but often misdiagnosed. Neurogenic mediators contribute to inflammation and immunosuppression following UV irradiation of the skin. The interaction between peripheral nerves and the immune system is mediated by different types of cutaneous nerve fibres that release neuromediators and activate specific receptors on target cells in the skin, such as keratinocytes, mast cells, Langerhans cells, microvascular endothelial cells, fibroblasts and infiltrating immune cells. Neuropeptides are capable of mediating cutaneous neurogenic inflammation by induction of vasodilation, plasma extravasation, and augmentation of cytokine, chemokine and cellular adhesion molecule expression. CRH is the most proximal element in the HPA axis, which coordinates the response to systemic stress and in peripheral organs modulates local immune and vascular functions, which together with UV radiation may be responsible for telangiectasia.[85]

Furthermore, CRH affects sebaceous lipogenesis.[86] Rosacea predominantly affects the centrofacial region that has a high density of seborrhoeic glands, such as cheeks, nose, chin and forehead. Altered sebum composition in rosacea patients[87] causes significantly decreased tolerogenic thymic stromal lymphopoietin levels and influx of inflammatory dendritic cells and T cells with IL-17/interferon-γ cytokine milieu, which may be one of the main events during rosacea development.[88]

### Beneficial effects of hormones

Hormones produced and metabolically activated or deactivated in human skin are probably important not only for skin functions but also for functions of the entire human organism. The skin is the site of vitamin D synthesis by UV B radiation providing beneficial effects on phosphor, calcium and bone metabolism, cellular proliferation and differentiation and immunity.

Female and male hormone replacement therapy (HRT) with exogenous systemic or topical oestradiol and DHEA can reverse or improve the cutaneous changes that result from the menopause and andropause.[89] Improvement in skin function parameters after 2–5 years HRT, compared to controls, includes hydration and sebum secretion, epidermal barrier lipids, sweat production, nail structure and skin texture, hair growth, skin distensibility and hysteresis and skin thickness.[90] However, it appears that principally sun-protected skin benefits from topical or systemic HRT rather than photoaged skin.[91,92]

Although the role of HRT has been widely debated over several decades, it now appears that when HRT is administered within 36 months of the last menstrual period in women aged 50–60 years old, proven benefits include the management of menopausal symptoms, reduced risk of osteoporotic fractures and improved quality of life, and it may be cardioprotective.[93] Conversely, in older postmenopausal women, the increased risk of developing an acute thrombotic event outweighs the benefits.

In men, population studies suggest that low serum levels of endogenous testosterone are a risk factor for cardiovascular events, but testosterone replacement therapy also increases the risk of cardiovascular disease.[94] There is a paucity of data on male HRT with other sexual hormones.

Dehydroepiandrosterone exerts its effects by a metabolic transformation into androgens and oestrogens via their specific nuclear receptors. A pilot study in two groups of 20 postmenopausal women showed that topical application of DHEA formulation (1%) for 4 months increased the sebum secretion rate and decreased skin atrophy compared to vehicle.[95] In a randomized controlled trial (RCT) of 60 women applying DHEA cream (0.3%, 1% or 2%) vs. placebo, topical DHEA increased the expression of several genes of the collagen family. The various pan-genomic changes induced by DHEA suggest that DHEA could exert an anti-ageing effect in the skin through stimulation of collagen in the dermis while modulating keratinocyte differentiation.[96] Androgen receptor expression was markedly increased by DHEA treatment and expression of heat shock protein 47 also increased, potentially affecting procollagen biosynthesis.[97]

Deleterious and beneficial effects of hormone levels on the skin are summarized in Table 2.

### Conclusions

Human skin is a major target of hormones, which can have an impact on several dermatoses, among them acne and rosacea. The physiological decline in hormones occurring with age plays a major role in skin ageing, which can to some extent be prevented and treated with HRT of oestradiol or DHEA.

## Section 4. Clinical and biological impact of nutrition on the skin

### Key points

- Dietary patterns, foods, nutrients and compounds may modify several biochemical processes, including oxidation, inflammation and glycation.
- Alterations in these processes may result in clinical effects, including modification of the course of skin ageing and photoageing, as well as potential impacts on acne, rosacea, AD and psoriasis.
- A large body of research, from animal and laboratory studies, short-term human intervention studies, long-term human intervention studies and large population studies, has identified biochemical, histologic and clinical effects of diet and dietary compounds.

### Impact of nutrient deficiencies and nutrient excess on the skin

The impact of the human diet on skin health has been recognized for centuries. Nutritional deficiencies such as scurvy and kwashiorkor certainly have significant effects on the skin. Cutaneous manifestations in malnourished patients with anorexia nervosa may include xerosis, lanugo-like body hair, telogen effluvium, acne, hyperpigmentation, seborrhoeic dermatitis, interdigital intertrigo, paronychia, acquired striae distensae and acral coldness[98].

Beyond classic nutrient deficiencies, however, nutrition has wide-ranging impacts on skin processes and conditions. Obesity

**Table 2** Deleterious and Beneficial Effects of Hormones on the Skin

| | Action | Conditions | References |
|---|---|---|---|
| ***Deleterious*** | | | |
| Almost all hormones, depending on the levels | Stimulates inflammation | Acne, rosacea | |
| Oestrogen (with a genetic predisposition and exposure to Ultraviolet radiation exposure) | Hyperpigmentation | Melasma | |
| IGF-1 in very high (clinically irrelevant) concentrations | Increases sebogenesis, epithelial cell proliferation and inflammation | Acne, rosacea | |
| Declining IGF-1 levels with age | Declining dermal collagen content, diminished skin moisture and consequently inflammation | Wrinkles, epidermal thinning, skin dryness | 66,67 |
| Declining sexual hormones: androgens, oestrogens and progestins | Cellular senescence, decreased proliferative cell capacity, chronic inflammation, mitochondrial DNA mutations and free radicals | Wrinkles, epidermal thinning, skin dryness, impaired wound healing, reduced vascularity and hot flashes | 65,68,71 |
| Neurohormones, e.g. corticotrophin-releasing hormone, released during chronic stress | Diminished keratinocyte and fibroblast function, inflammation, altered sebum composition | Rosacea, skin ageing, pigmentation, poor thermoregulation | 76–78 |
| Increased androgen levels, hydrocortisone | Sebaceous lipogenesis, inflammation, *Propionibacterium acnes* colonization | Acne | 80 |
| ***Beneficial*** | | | |
| Hormones metabolically activated or deactivated in human skin | Multiple functions in the skin and the entire body | Multiple health benefits | 62 |
| Calcitriol (vitamin D) | Synthesized in the skin in the presence of ultraviolet light | Multiple health benefits, especially healthy bones | |
| Oestradiol | Hormone replacement therapy | Improves the cutaneous changes due to the menopause, reduction in osteoporosis, improves quality of life, cardiovascular benefits | 89,90 |
| Dehydroepiandrosterone | Hormone replacement therapy | Improves the cutaneous changes due to the menopause or andropause | 89,95–97 |
| Testosterone | Hormone replacement therapy | Improves the cutaneous changes due to the andropause (pigmentation, thinning, wound healing, hair growth) | 94 |

has been associated with system-wide metabolic dysfunction, while caloric restriction is associated with a distinct metabolic state, suggesting that adipose tissue signalling may be a potential target for interventions to delay ageing.[99]

Dietary factors may modify the process of skin ageing, affect skin tumorigenesis or impact the clinical course of various skin diseases including AD, psoriasis, acne and rosacea.

### How dietary patterns and compounds modify biochemical processes

A large body of research has demonstrated the effects of dietary patterns, foods, nutrients and other dietary compounds on specific biochemical processes.[100] These processes, which include oxidation, inflammation and glycation, result in clinical changes to the skin structure and function. Other effects of dietary compounds include impacts on endogenous DNA repair systems, changes in hormone levels, systemic effects and changes to the composition of the gut microbiome. There is increasing evidence connecting skin conditions with the gastrointestinal microbiome and the potential role played by dietary compounds across the gut–skin axis.[101]

### Research approaches to study the impact of nutrition on the skin

Population cohort studies and long-term human interventional studies provide data on long-term effects. The field of nutritional epidemiology tends to focus on the study of dietary patterns, while interventional studies may examine the effects of dietary patterns or individual nutrients. Short-term human experimental studies help clarify the effects of single nutrients or compounds, while animal and laboratory studies help delineate the effects of diet on biochemical processes. Taken together, this large body of research demonstrates that diet has significant effects on the skin.

### Impact of nutrition on skin ageing and photoageing

Skin ageing and photoageing provide a well-studied model to demonstrate the relationship between diet, biochemical processes and clinical effects. Several epidemiologic studies have demonstrated that people who adhere to healthier eating patterns exhibit less clinical signs of skin ageing. In 2753 elderly Dutch individuals, better adherence to the Dutch healthy guidelines was significantly associated with fewer wrinkles in women.[102] Conversely, a dietary pattern dominated by red meat and snacks was associated with more facial wrinkles. Another study evaluated the estimated age of over 500 non-diabetic subjects and compared this to glucose levels.[103] Even after accounting for degree of sun damage, smoking, weight and other factors, it was found that perceived age increased as blood glucose levels increased.

A review of the pathogenesis of skin ageing provides some potential explanations. Skin ageing and photoageing are due to a complex and intertwined number of biochemical processes, including oxidation, inflammation and glycation, among others. Importantly, dietary compounds have a significant impact on each of these major processes.

Ultraviolet radiation exposure is a major factor in skin ageing and produces a cascade of effects in the skin.[104] The accumulation of DNA damage, oxidative stress and the production of free radicals, and local immunosuppression all contribute to tumorigenesis.[105] While endogenous antioxidants act to neutralize free radicals, they must be constantly replenished by dietary sources.

*Dietary antioxidants* Studies have reported protective benefits from nutrients including lycopene, beta-carotene, astaxanthin and probiotics, as well as foods including tomatoes, green tea, pomegranate, cocoa and other polyphenols.[106,107]

While dietary antioxidants (AOs) are critical in battling the effects of oxidative stress, they must be the right dose, ideally physiologic doses, such as that supplied via whole foods. Despite promising laboratory and animal studies, multiple RCTs of high-dose AO supplements including vitamins C and E, beta-carotene and selenium have not shown efficacy in non-melanoma skin cancer (NMSC) prevention.[105] In fact, evidence indicates that the dose of AOs is important as they could become pro-oxidant at high doses. In one large study with median follow-up of 7.5 years, women (but not men) consuming a supplement, containing high doses of vitamin C, vitamin E, beta-carotene, selenium and zinc, exhibited higher rates of skin cancer.[108]

*Dietary compounds that impact inflammatory processes* Dietary compounds are also known to impact inflammatory processes. In one large analysis of over 1900 studies that evaluated the effects of foods and nutrients on major biomarkers of inflammation, nutrients that increased levels of IL-1B, IL-6, TNF-alpha or C-reactive protein, or decreased levels of IL-4 or IL-10, were considered pro-inflammatory.[109] Using these results, researchers developed a dietary inflammatory index, with foods and nutrients that scored higher, acting to mitigate the damaging effects of inflammation. Some phytochemicals may specifically interrupt the inflammatory pathway that activates nuclear transcription factor kappa-beta, including turmeric, cloves, ginger, garlic and others.[110] Other foods and nutrients have demonstrated abilities to block the action of MMPs such as collagenase, including plant extracts of green tea, white tea and pomegranate.[111] The natural flavonoid quercetin was found to be a strong inhibitor of collagenase;[112] quercetin is naturally found in certain foods such as onions and cauliflower.

*Dietary patterns that impact glycation* Glycation and resultant collagen damage also contribute significantly to the clinical signs

of skin ageing. Glycation refers to the non-enzymatic bonding of sugars to proteins, which results in the production of advanced glycation end products (AGEs) and affects the cross-linking of collagen fibres. This results in loss of skin elasticity, colloquially known as sugar sag, as well as loss of elasticity within blood vessel walls, predisposing to hypertension and cardiovascular disease.

Dietary patterns that promote hyperglycaemia are a major contributor to the production of AGEs, and patients are advised to limit added sugars and processed carbohydrates. However, dietary advice must always be individualized. In a classic example of how genetic variations and multiple other factors impact an individual's response to the same environmental factor, researchers in Israel studied the effects of a standardized dose of carbohydrates on blood glucose measurements. Using continuous glucose monitoring in over 800 non-diabetic individuals, researchers found a marked difference in blood glucose response to the same exact dose of carbohydrates.[113]

The other contribution to the overall load of AGEs is via ingestion of preformed AGEs. Research has demonstrated that certain foods contain higher levels of preformed AGEs[114] and that these may be absorbed from the gut. As a general rule, meats and fats contain higher levels of AGEs, while fruits, vegetables, grains and milk contain lower levels. The type of cooking method also has a significant effect, as dry heat methods such as roasting, broiling and grilling may increase AGE formation by 10- to 100-fold. These methods do not have the same degree of impact on fruits and vegetables. Moist cooking methods and cooking at lower temperatures for shorter times are preferred.

*Dietary compounds that support DNA repair mechanisms* Another avenue by which dietary compounds may prove helpful is via their support of DNA repair mechanisms. Given the constant threats posed by UV radiation and free radical production, the skin has a complex system of built-in repair mechanisms. Nutrients may help support DNA repair, as in the case of nicotinamide which appears to work by preventing the depletion of cellular $NAD^+$ levels which results from the repair process, with a corresponding boost in cellular energy. In one RCT, patients at high risk of skin cancer and taking nicotinamide had 23% lower rates of new NMSC as compared to controls.[115]

### Impact of nutrition on dermatoses

Several dermatoses highlight other pathways by which nutrition impacts clinical findings.

*Acne* Diet-induced metabolic changes, metabolic syndrome and obesity play a role in some patients with acne.[83] In acne, dietary patterns that promote hyperglycaemia may trigger hormonal changes that trigger inflammatory pathways.[83,116] An RCT of a low glycaemic index diet for 12 weeks resulted in a greater decrease in total lesion counts, while serum studies indicated an increase in IGF-binding protein and a reduction of the free androgen index.[117] Later studies of the same intervention demonstrated decrease in skin sebum, androgen bioavailability and by histology, decreased skin inflammation and sebaceous gland size.[118] Patients should be advised to balance total calorie uptake and restrict refined carbohydrates, dairy protein supplements, saturated fats, trans-fats and possibly dairy in some individuals.[116]

*Rosacea* In rosacea, dietary compounds that affect specific structures in the body may play a role. One area of study is the effect of compounds on blood vessel function, an important factor in rosacea pathogenesis. Although research is limited, patients surveyed by the National Rosacea Society frequently identify certain foods as potential triggers.[119] These foods include hot beverages and alcohol, which are known vasodilators. Other foods include those that contain capsaicin, such as spicy foods, and those that contain cinnamaldehyde, including tomatoes, citrus and chocolate. Research has identified capsaicin and cinnamaldehyde as triggers of transient receptor potential channels, which when activated result in neurogenic vasodilatation.[120]

*Atopic dermatitis* Another area of study is the role of dietary measures that support the gut microbiome in inflammatory dermatoses such as AD. Although the gut–skin axis is not fully understood, emerging evidence indicates that the gut and skin microbiome could be manipulated to treat AD. A meta-analysis of six studies concluded that the use of synbiotics in adults and children over the age of 1 year may be helpful in the treatment of AD.[101] Synbiotics are a combination of prebiotics, which promote the growth of beneficial gut microbes, and probiotics, which are defined as live microorganisms which when ingested provide benefit. These are of interest as research has indicated that a healthier gut microbiome may provide protective effects against allergic and inflammatory disorders, and those with AD may have an altered gut microbiota.[101] Dietary measures that support the gut microbiome include an emphasis on prebiotic foods, i.e. those that are naturally rich in fibre. In terms of supplementation, many questions remain, as studies have shown a wide difference in individual response as well as using differing doses, duration and even composition of studied prebiotic and probiotic supplements.

*Psoriasis* The importance of dietary modification in psoriasis is well-known, given the risk of systemic comorbidities. A large body of research has demonstrated that patients with psoriasis are at higher risk for multiple comorbidities, including obesity, diabetes, dyslipidaemia, hypertension and

cardiovascular disease.[121] While the pathogenesis behind this link has not been fully elucidated, one area of study is the link between skin inflammation and systemic inflammation. Obesity may also play a role in promoting systemic inflammation, and in fact, multiple RCTs have demonstrated that weight loss in overweight or obese psoriasis patients may improve both psoriasis severity scores and response to systemic therapies. In evaluating over 55 studies, the authors concluded that weight loss in overweight or obese psoriasis patients is strongly recommended.[122]

### Beneficial and deleterious effects of nutrition on the skin

Beneficial and deleterious effects of dietary patterns, foods and nutrients are illustrated in Table 3.

### Conclusions

Dietary patterns, foods, nutrients and compounds impact many biochemical processes and may beneficially or detrimentally modify the course of skin ageing, or impact various dermatoses, including acne, rosacea, AD and psoriasis.

## Section 5. Clinical and biological impact of psychological factors on the skin

### Key points

- Sleep deprivation and stress are known to contribute to a pro-inflammatory state, which, in turn, affects the integrity of extracellular matrix proteins, in particular collagen.
- Several studies of prolonged sleep deprivation also suggest a break in skin barrier function and mucous membranes indicating that sleep loss can lead to skin damage and affect healing processes.
- Psychological stress can exacerbate or trigger several inflammatory, autoimmune and allergic skin diseases.
- Inflammatory skin disorders, such as AD, psoriasis, acne and rosacea, may be affected by stress.

**Table 3** Beneficial and deleterious effects of nutrition on the skin

| Dietary pattern, food, nutrient or compound | Action | Skin condition | References |
|---|---|---|---|
| ***Beneficial*** | | | |
| Fruit-dominant healthy diet | Antioxidant, anti-inflammatory, low glycaemic load | Fewer wrinkles | 102 |
| Phytochemical derivatives, including polyphenols (e.g. tea, cocoa, grape, soy, pomegranate) and non-polyphenols (e.g. carotenoids, caffeine) | Antioxidant, anti-inflammatory and immunomodulatory effects | Photoageing and photocarcinogenesis | 106 |
| Carotenoids (e.g. tomatoes) | Antioxidant | Photoageing and photocarcinogenesis | 107 |
| Dietary pattern emphasizing whole foods | Antioxidant, anti-inflammatory | Non-melanoma skin cancer | 105 |
| Plant extracts (e.g. white tea) | Antioxidant and anticollagenase | Ageing | 111 |
| Spice-derived phytochemicals | Anti-inflammatory | Skin cancer, inflammatory diseases | 110 |
| Synbiotics, fibre-rich (prebiotic) diet | Promotes beneficial gut microbes | Atopic dermatitis, rosacea | 101,120 |
| Fish and omega-3 fatty acids | Anti-inflammatory | Atopic dermatitis, psoriasis, acne | 123 |
| Nicotinamide, vitamin $B_3$ (liver, meats, yeast, legumes, nuts, green leafy vegetables, cereals, tea and coffee) | Promotes DNA repair | Non-melanoma skin cancer, actinic keratosis | 115 |
| ***Deleterious*** | | | |
| High-dose supplements (vitamin C, vitamin E, beta-carotene, selenium, zinc) | Oxidant | Skin cancer (in women) | 105,108 |
| Sugar, high glycaemic load diet, excess food intake | Hyperglycaemia and systemic inflammation | Acne, psoriasis, ageing | 83,121,122 |
| Sugars and processed carbohydrates | Hyperglycaemia | More wrinkles and 'sugar sag' | 102,103 |
| Diet rich in heat-processed meats and fats (preformed advanced glycation end products) | Oxidant stress and inflammation | Wound healing, ageing, inflammatory conditions | 114 |
| Hot beverages, alcohol, cinnamaldehyde, capsaicin | Vasodilation | Rosacea triggers | 119,120 |
| Dioxin-contaminated foods (meat and dairy products, fish and shellfish) | Organic pollutants affecting a number of organs and systems | Skin cancer, chloracne | 124 |

### Sleep deprivation and stress in modern society

Sleep quality has declined over recent decades in many countries, especially in modern industrialized societies, with an increase in sleep complaints and disturbances, e.g. snoring, nightmares, bruxism, leg cramps, somnambulism, sleep paralysis and excessive daytime somnolence. In particular, obstructive sleep apnoea (OSA) and insomnia are highly prevalent among men and women, respectively, and both cause sleep deprivation. Fortunately, there are several approaches to treat them.

### Stress and psychiatric problems contribute to sleep deprivation

Sleep is one of the major components of health-related quality of life.[125] Indeed, complaints about sleep are frequent among individuals who are under stress. In addition, poor sleep may be associated with psychiatric disorders. Psychosocial aspects can influence sleep, and primary insomnia is related to anxiety and depression. Sleep deprivation and stress is a vicious cycle since stress causes an increase in levels of cortisol, which causes late sleep onset.

### Effect of sleep deprivation and stress on skin

The skin plays a fundamental role in the regulation of homeostasis, and its location between external and internal environments determines its structural and functional organization, being vulnerable to several stressors.[126] The impact of psychosocial stress on healthy skin and the varied roles of the major cutaneous stress response pathways have been reviewed by Hunter *et al.*[127] As sleeping is critical for cellular growth and renovation, sleep deprivation and poor sleep quality lead to cellular dysfunction due to circadian rhythm disruption and therefore have many effects on the body, inducing changes in the skin.

Stress, an inherent factor in the lack of sleep, is known to contribute to a pro-inflammatory state, which, in turn, affects the integrity of collagen fibres through glucocorticoid-mediated processes that alter its synthesis and degradation (see review by Kahan *et al.*[128]). Sleep deprivation leads to hyperactivation of the HPA axis, mostly by increasing the production of corticosterone and adrenocorticotropic hormone, which adversely affect skin integrity.[129] Cortisol and pro-inflammatory cytokines, such as IL-8 and TNF-α, impair the production of collagen and other skin proteins, increase the activity of MMPs, and promote water loss and DNA damage.[128]

The immune response can alter the normal sleep pattern, while sleep loss can adversely affect the immune response related to graft rejection. Using a skin allograft model in mice, it was shown that numbers of total T cells, CD4 T cells and CD8 T cells in the lymph nodes and spleen were higher after undisturbed sleep than after prolonged sleep restriction, which was accompanied by increased allograft rejection.[130]

### Impact of sleep deprivation and stress on skin ageing

There is a paucity of studies on the effect of psychological factors on skin ageing. In one study on elderly, female hairless mice, lack of sleep (72 h of paradoxical sleep deprivation or 15 days of chronic sleep restriction) had no effect on DNA damage in the skin.[131]

No clinical study has demonstrated a clear relationship between sleep deprivation or stress on human skin function and visible signs of ageing. However, it has been demonstrated that women classified as good sleepers (sleep duration of 7–9 h according to the Pittsburgh Sleep Quality Index questionnaire) presented fewer signs of intrinsic skin ageing, a greater rate of recovery from erythema after solar-simulating radiation and a 30% greater barrier recovery in comparison with those considered as poor sleepers with 5 h or less of sleep.[132]

### Impact of sleep deprivation on facial appearance

In an interventional crossover study, patients with severe OSA were randomized to receive either continuous positive airway pressure (CPAP) treatment or nasal dilator (placebo) for 1 month.[133] Results from questionnaires, polysomnography and facial photographs indicated that patients had a younger appearance following 1 month of CPAP treatment compared to placebo.

Interestingly, in a recent study investigating the effect of sleep deprivation on both objective and subjective measures of facial appearance, in a between-subject design (raters were presented with just one image of each subject either sleep deprived or well rested), no significant differences in facial appearance and skin colour were observed after one night of total sleep deprivation.[134]

### Impact of stress on dermatoses and comorbidities

Psychological stress can exacerbate or trigger several skin disorders, and it is known to have a modulator effect on the pathophysiology of several inflammatory, autoimmune and allergic diseases.[135] Chronic stress (psychological stress or medical stress, for example, surgery or pregnancy) may play a role in the increase of inflammatory cytokines associated with an immunosuppressor status of increased risk of infectious diseases. Stress leads to the activation of several signals in the central nervous system. The neuroendocrine response results in the release of adrenal steroid hormones, such as corticosterone, via the HPA axis, whereas the autonomous nervous system response leads to the release of catecholamines, especially norepinephrine (NE), by the sympathetic nerve termini.[136,137] A growing body of research suggests neuropeptides and neurotransmitters, released by nerves innervating the skin, have important regulatory activities on antigen presentation, mast cell function and endothelial cell biology, thereby influencing cutaneous immunity.[138] The effects of stress in the skin are represented by the activation of dendritic cells and

neuromediator catecholamine release by cutaneous nerve endings.[139] A close relationship between the nervous system, stress and inflammatory skin disorders, such as AD, acne and rosacea, is widely accepted, and this neurophysiological modulation may contribute to the exacerbation of other diseases, such as psoriasis and vitiligo. A vicious cycle may arise as stress might exacerbate the skin condition, which may in turn perpetuate or increase psychological stress.

*Psoriasis* The relationship between psoriasis and stress is complex. Chronic stress suppresses the negative feedback of the HPA, leading to elevated levels of corticotropin-releasing hormone (CRH) and glucocorticoids (GC), which play a role in the aetiopathogenesis of inflammatory skin diseases, such as psoriasis.[140] This scenario also might develop an imbalance of oxidative free radicals followed by DNA damage.

Although the clinical significance has not been fully elucidated, a Danish nationwide cohort study found that psoriasis was associated with increased OSA and OSA was associated with increased risk of psoriasis.[141] A study in male adult Balb/C mice with or without psoriasis subjected to 48 h of selective paradoxical sleep deprivation showed that sleep deprivation plays an important role in the exacerbation of psoriasis through modulation of cytokine and stress-related hormone levels in the epidermal barrier. Thus, sleep loss should be considered a risk factor for the development of psoriasis (for review, see Hirotsu *et al.*[142]). Interestingly, immunological activities and pro-inflammatory cytokines play a prominent role in both OSA and psoriasis.[143]

*Acne* Two large-scale epidemiological studies using self-administered questionnaires conducted in 3305 women in France[144] and in 1236 patients in Korea[145] indicated that stress, lack of sleep and menstruation aggravate acne.

In recent years, the prevalence of adult female acne has increased possibly due to the increased social pressure on women in modern society leading to stress and sleep deprivation.[146] Acne is aggravated by stress and sleep deprivation, which increases cortisol and inflammation. Immunohistochemical data have shown that stress neuropeptides, such as the CRH system and melanocortin-1 receptor, are key regulators of sebaceous gland activity and are involved in the pathogenesis of acne.[147] CRH upregulates 3β-hydroxysteroid dehydrogenase at the mRNA level in human SZ95 sebocytes, thus promoting lesional steroidogenesis and subsequently androgen excess, which causes acne.

A randomized comparative trial evaluating the effect of combined oral contraceptive (COC) or azelaic acid (AA) on sleep quality in adult female acne patients demonstrated that after 6-month treatment, the AA group presented better subjective sleep quality; the efficacy on treating acne was similar for both groups.[148] In addition, higher levels of morning cortisol and lower levels of free testosterone were observed in the COC group than the AA group. The authors suggested that sleep quality improved in the AA group since treatment of the lesions decreased discomfort, while improving facial appearance, quality of life and, consequently, sleep.

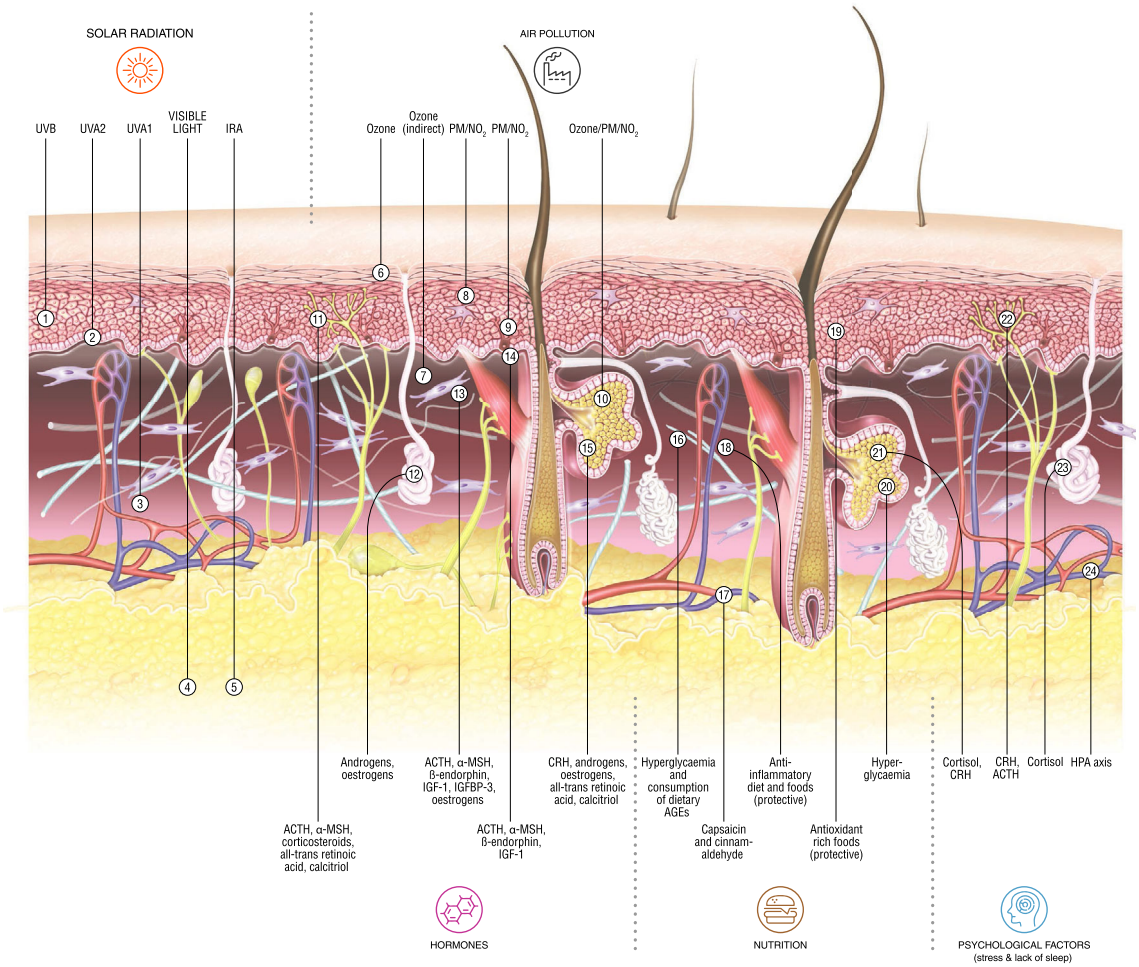
*Rosacea* Rosacea is a chronic relapsing inflammatory skin disease thought to involve dysregulation of innate and adaptive immune pathways as well as neurovascular changes.[149] Psychological stress is the second most common trigger reported by rosacea patients and may exacerbate symptoms. Stress may be implicated in the pathology of rosacea since it is known to activate both neuronal and inflammatory pathways.[150] Repeated psychological stress can induce a chronic immune reaction and elevation of cytokines, which may perpetuate inflammatory processes.

*Atopic dermatitis* The onset, progression and severity of AD are known to be influenced by stress, even if the precise immune mechanisms involved are not fully understood. Psychological stress can trigger the development of AD-like skin lesions in mice, and this could be blocked by CRH-antagonist treatment.[151] Chronic stress causing a blunted HPA axis response has been reported to aggravate allergic diseases due to the lack of immunosuppressive effects of low cortisol levels and enhanced Th2 response.[152] Prenatal maternal distress has been predicted to increase AD risk in offspring, possibly involving chronic stress, abnormal steroid levels and ROS.[153]

There are a number of potential risk factors for sleep disturbance in AD patients, including the itch–scratch cycle, poor sleep hygiene, circadian rhythm-induced modification of itch and secondary effects of inflammatory cytokines on sleep regulation.[154] Sleep disturbance and itch both significantly impair the quality of life of patients. The association between AD and neuropsychiatric conditions has been widely studied, with an increased risk of mental health disorders strongly influenced by sleep disorders, and severe AD has been linked with increased prevalence of both anxiety and sleep disorder.[155] An observational case–control study found that patients with inflammatory skin disorders (chronic AD, contact dermatitis and psoriasis) had significantly more fatigue and higher odds of insomnia compared to patients with non-inflammatory conditions (basal cell or squamous cell skin cancers).[156]

*Vitiligo and alopecia areata* Vitiligo and alopecia areata are both well-demonstrated autoimmune disorders with striking similarities in pathogenesis at the level of both the innate and adaptive immune systems. Genetic, immune and oxidative stress factors have been implicated in both diseases, and possible triggers include physical/emotional stress, infections and hormones. Evidence is increasing regarding the role of neuropeptides, such




**SOLAR RADIATION**

1. **EPIDERMIS:** keratinocytes + melanocytes
2. **EPIDERMIS:** keratinocytes + melanocytes
3. **DERMIS:** fibroblasts + endothelial cells
   **EPIDERMIS:** melanocytes
4. **HYPODERMIS + DERMIS + EPIDERMIS:** melanocytes (high energy visible light only)
5. **HYPODERMIS** (reticular dermis) **+ DERMIS + EPIDERMIS**

**AIR POLLUTION**

6. **STRATUM CORNEUM**
7. **DERMIS**
8. **KERATINOCYTES**
9. **MELANOCYTES**
10. **SEBACEOUS GLAND CELLS**

**HORMONES**

11. **KERATINOCYTES**
12. **SWEAT GLAND**
13. **FIBROBLASTS**
14. **MELANOCYTES**
15. **SEBACEOUS GLAND CELLS**

**NUTRITION**

16. **COLLAGEN FIBRES**
17. **BLOOD VESSELS**
18. **DERMIS AND EXTRACELLULAR MATRIX**
19. **EPIDERMIS**
20. **SEBACEOUS GLAND CELLS**

**PSYCHOLOGICAL FACTORS (stress & lack of sleep)**

21. **SEBACEOUS GLAND CELLS**
22. **NERVE ENDINGS**
23. **SWEAT GLAND**
24. **BLOOD VESSELS**

**Abbreviations:** UV ultraviolet; IRA Infrared A; $NO_2$ nitrogen dioxide; PM particulate matter; ACTH adrenocorticotrophic hormone; α-MSH alpha-melanocyte-stimulating hormone; IGF-1, insulin-like growth factor-1; CRH corticotrophin-releasing hormone; IGFBP-3 insulin-like growth factor binding protein-3; AGEs advanced glycation end products; HPA hypothalamic-pituitary-adrenal.

**Figure 3a**

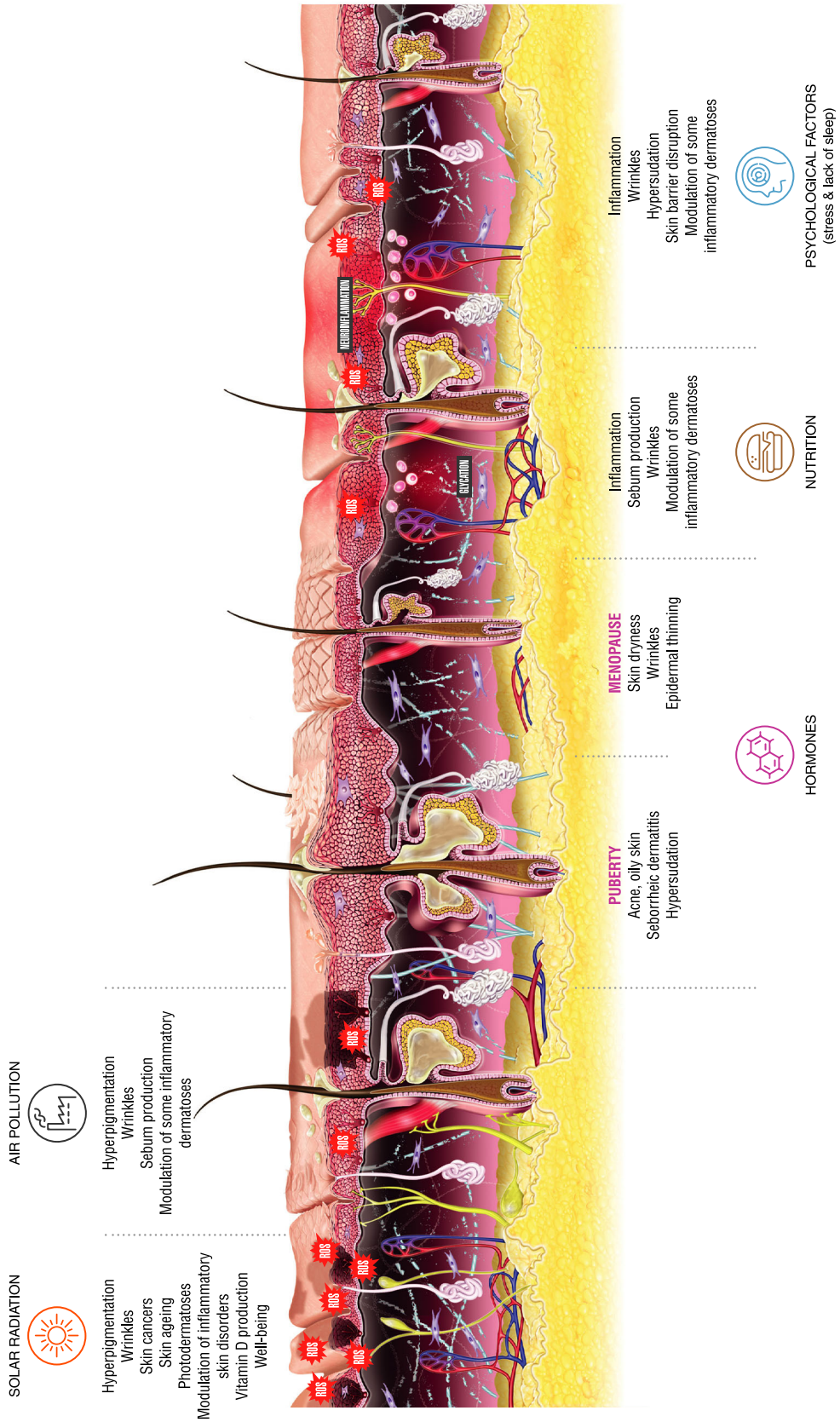



**Figure 3b**

**Figure 3a and 3b** The main impact on the skin (a) and the main effects (b) of the individual exposome factors of solar radiation, air pollution, hormones, nutrition and psychological factors (stress and lack of sleep). The depth of penetration into the different layers of the skin is dependent on the wavelength of solar radiations. UVB and UVA2 mostly impact the epidermis; UVA1 also affect the dermis, while VL and IRA penetrate up to the hypodermis and thus could potentially impact all the compartments of the skin. UVB modulates the immune response by acting on dendritic cells and lymphocytic infiltrates, inducing direct DNA damage on keratinocytes and melanocytes and stimulating pigmentation. Short-wave UVA (UVA2) also mostly affects the epidermis, while long-wave UVA (UVA1) affects also fibroblasts and endothelial cells, mostly by inducing oxidative stress. Visible light and short infrared (IRA) penetrate even deeper, reaching the reticular dermis and the hypodermis. In addition to the production of oxidative species, some of these wavelengths also induce biological effects through the direct activation of specific sensors. Air pollution can be due to particulate matter, ozone and nitrogen dioxide. The impact of these environmental factors on the skin is not yet fully understood. Soot, fine particulate matter and possibly nitrogen dioxide induce pigment spots/melanin synthesis (potentially by acting on p53), while ozone promotes wrinkle formation (possibly through the activation of AhR and oxidative stress formation). The skin is itself an endocrine organ. All its components are constantly regulated by hormones (epidermis, dermis, but also sebaceous glands, hair follicles and vascularization). Hormones can affect cellular senescence, free radicals, sebum production, and inflammation and participate in skin ageing and modulate skin dermatoses. Hormone-like effective compounds, defined as endocrine-disrupting chemicals, can perturb the endocrine system. Nutrition has a wide-ranging impact on skin processes and conditions, and may cause deleterious or beneficial effects. Quantitative or qualitative defects, ranging from obesity, caloric restriction, the ingestion of pro-inflammatory nutrients, processed carbohydrates and advanced glycation end products (deleterious) to the ingestion of dietary antioxidants, prebiotics and other dietary factors (beneficial), may modify the process of skin ageing, affect skin tumorigenesis or impact the clinical course of multiple skin diseases. Stress contributes to a pro-inflammatory state that can induce the degradation of the extracellular matrix or modulate the course of skin diseases such as atopic dermatitis, psoriasis, acne or rosacea. Stress is an inherent factor of lack of sleep. Prolonged sleep deprivation can alter the healing processes of the skin and the immune response and promote matrix degradation.

as substance P, and crosstalk between the systemic HPA axis and local HPA axis with cytokine production of the skin.[157,158]

### Conclusions and perspectives

Interest is growing in the psychological aspects of skin diseases. As most skin conditions are readily visible, they can significantly impair quality of life and can have severe detrimental psychological effects even when not related to pain and discomfort. On the other hand, skin reacts to psychological factors and they can cause or aggravate certain skin conditions. However, psychological factors are currently one of the least well-studied exposome factors. Interventional studies are required to evaluate the impact on the skin of sleep disorders and other psychological disorders. Polysomnography, although expensive, is considered the gold standard for objectively measuring sleep quality in the laboratory setting in humans; it can be used with validated questionnaires to assess psychiatric disease symptoms, stress and sleep quality.

## Section 6. Summary of individual exposome factors on the skin at the cellular level

Figure 3 illustrates the main impact on the skin (Fig. 3a) along with the main effects (Fig. 3b) of the individual exposome factors of solar radiation, air pollution, hormones, nutrition and psychological factors (stress and lack of sleep).

## Acknowledgements

Medical writing and editorial assistance for the preparation of this manuscript were provided by Helen Simpson, PhD, of My Word Medical Writing.

## References

1 D'Orazio J, Jarrett S, Amaro-Ortiz A, Scott T. UV radiation and the skin. *Int J Mol Sci* 2013; **14**: 12222–12248.
2 Emri G, Paragh G, Tosaki A *et al*. Ultraviolet radiation-mediated development of cutaneous melanoma: an update. *J Photochem Photobiol B* 2018; **185**: 169–175.
3 Krutmann J, Bouloc A, Sore G, Bernard BA, Passeron T. The skin aging exposome. *J Dermatol Sci* 2017; **85**: 152–161.
4 Parrado C, Mercado-Saenz S, Perez-Davo A, Gilaberte Y, Gonzalez S, Juarranz A. Environmental stressors on skin aging. Mechanistic insights. *Front Pharmacol* 2019; **10**: 759.
5 Amano S. Characterization and mechanisms of photoageing-related changes in skin. Damages of basement membrane and dermal structures. *Exp Dermatol* 2016; **25**(Suppl 3): 14–19.
6 Liebel F, Kaur S, Ruvolo E, Kollias N, Southall MD. Irradiation of skin with visible light induces reactive oxygen species and matrix-degrading enzymes. *J Invest Dermatol* 2012; **132**: 1901–1907.
7 Grether-Beck S, Marini A, Jaenicke T, Krutmann J. Effective photoprotection of human skin against infrared A radiation by topically applied antioxidants: results from a vehicle controlled, double-blind, randomized study. *Photochem Photobiol* 2015; **91**: 248–250.
8 Albrecht S, Jung S, Muller R *et al*. Skin type differences in solar-simulated radiation-induced oxidative stress. *Br J Dermatol* 2019; **180**: 597–603.
9 Fajuyigbe D, Lwin SM, Diffey BL *et al*. Melanin distribution in human epidermis affords localized protection against DNA photodamage and concurs with skin cancer incidence difference in extreme phototypes. *FASEB J* 2018; **32**: 3700–3706.
10 Fajuyigbe D, Young AR. The impact of skin colour on human photobiological responses. *Pigment Cell Melanoma Res* 2016; **29**: 607–618.
11 Miyamura Y, Coelho SG, Wolber R *et al*. Regulation of human skin pigmentation and responses to ultraviolet radiation. *Pigment Cell Res* 2007; **20**: 2–13.
12 Marionnet C, Nouveau S, Hourblin V *et al*. UVA1-induced skin darkening is associated with molecular changes even in highly pigmented skin individuals. *J Invest Dermatol* 2017; **137**: 1184–1187.

13 Mahmoud BH, Ruvolo E, Hexsel CL *et al*. Impact of long-wavelength UVA and visible light on melanocompetent skin. *J Invest Dermatol* 2010; **130**: 2092–2097.
14 Duteil L, Cardot-Leccia N, Queille-Roussel C *et al*. Differences in visible light-induced pigmentation according to wavelengths: a clinical and histological study in comparison with UVB exposure. *Pigment Cell Melanoma Res* 2014; **27**: 822–826.
15 Regazzetti C, Sormani L, Debayle D *et al*. Melanocytes sense blue light and regulate pigmentation through opsin-3. *J Invest Dermatol* 2018; **138**: 171–178.
16 Passeron T. The key question of irradiance when it comes to the effects of visible light in the skin. *J Dermatol Sci* 2019; **93**: 69–70.
17 Duteil L, Queille-Roussel C, Lacour JP, Montaudie H, Passeron T. Short term exposure to blue light emitted by electronic devices does not worsen melasma. *J Am Acad Dermatol* 2019; S0190-9622(19)33324-9. https://doi.org/10.1016/j.jaad.2019.12.047.
18 Passeron T, Picardo M. Melasma, a photoaging disorder. *Pigment Cell Melanoma Res* 2018; **31**: 461–465.
19 Boukari F, Jourdan E, Fontas E *et al*. Prevention of melasma relapses with sunscreen combining protection against UV and short wavelengths of visible light: a prospective randomized comparative trial. *J Am Acad Dermatol* 2015; **72**: 189–190.e1.
20 Martini APM, Maia CP. Influence of visible light on cutaneous hyperchromias: clinical efficacy of broad-spectrum sunscreens. *Photodermatol Photoimmunol Photomed* 2018; **34**: 241–248.
21 Passeron T, Nouveau S, Duval C *et al*. Development and validation of a reproducible model for studying post-inflammatory hyperpigmentation. *Pigment Cell Melanoma Res* 2018; **31**: 649–652.
22 Kohli I, Chaowattanapanit S, Mohammad TF *et al*. Synergistic effects of long-wavelength ultraviolet al and visible light on pigmentation and erythema. *Br J Dermatol* 2018; **178**: 1173–1180.
23 Shnitkind E, Yaping E, Geen S, Shalita AR, Lee WL. Anti-inflammatory properties of narrow-band blue light. *J Drugs Dermatol* 2006; **5**: 605–610.
24 Sardana K, Sharma RC, Sarkar R. Seasonal variation in acne vulgaris–myth or reality. *J Dermatol* 2002; **29**: 484–488.
25 Adityan B, Thappa DM. Profile of acne vulgaris–a hospital-based study from South India. *Indian J Dermatol Venereol Leprol* 2009; **75**: 272–278.
26 van Zuuren EJ. Rosacea. *N Engl J Med* 2017; **377**: 1754–1764.
27 Wolf P, Weger W, Patra V, Gruber-Wackernagel A, Byrne SN. Desired response to phototherapy vs photoaggravation in psoriasis: what makes the difference? *Exp Dermatol* 2016; **25**: 937–944.
28 Ellenbogen E, Wesselmann U, Hofmann SC, Lehmann P. Photosensitive atopic dermatitis–a neglected subset: clinical, laboratory, histological and photobiological workup. *J Eur Acad Dermatol Venereol* 2016; **30**: 270–275.
29 Garmyn M, Young AR, Miller SA. Mechanisms of and variables affecting UVR photoadaptation in human skin. *Photochem Photobiol Sci* 2018; **17**: 1932–1940.
30 Juzeniene A, Moan J. Beneficial effects of UV radiation other than via vitamin D production. *Dermatoendocrinol* 2012; **4**: 109–117.
31 Fell GL, Robinson KC, Mao J, Woolf CJ, Fisher DE. Skin beta-endorphin mediates addiction to UV light. *Cell* 2014; **157**: 1527–1534.
32 Weller RB. Sunlight has cardiovascular benefits independently of vitamin D. *Blood Purif* 2016; **41**: 130–134.
33 Romero-Graillet C, Aberdam E, Clement M, Ortonne JP, Ballotti R. Nitric oxide produced by ultraviolet-irradiated keratinocytes stimulates melanogenesis. *J Clin Invest* 1997; **99**: 635–642.
34 Fang FC. Perspectives series: host/pathogen interactions. Mechanisms of nitric oxide-related antimicrobial activity. *J Clin Invest* 1997; **99**: 2818–2825.
35 Felton S, Navid F, Schwarz A, Schwarz T, Glaser R, Rhodes LE. Ultraviolet radiation-induced upregulation of antimicrobial proteins in health and disease. *Photochem Photobiol Sci* 2013; **12**: 29–36.
36 Janich P, Toufighi K, Solanas G *et al*. Human epidermal stem cell function is regulated by circadian oscillations. *Cell Stem Cell* 2013; **13**: 745–753.
37 Vierkötter A, Schikowski T, Ranft U *et al*. Airborne particle exposure and extrinsic skin aging. *J Invest Dermatol* 2010; **130**: 2719–2726.
38 Gao W, Tan J, Hüls A *et al*. Genetic variants associated with skin aging in the Chinese Han population. *J Dermatol Sci* 2017; **86**: 21–29.
39 Ding A, Yang Y, Zhao Z *et al*. Indoor PM2.5 exposure affects skin aging manifestation in a Chinese population. *Sci Rep* 2017; **7**: 15329.
40 Hüls A, Vierkötter A, Gao W *et al*. Traffic-related air pollution contributes to development of facial lentigines: further epidemiological evidence from Caucasians and Asians. *J Invest Dermatol* 2016; **136**: 1053–1056.
41 Li M, Vierkötter A, Schikowski T *et al*. Epidemiological evidence that indoor air pollution from cooking with solid fuels accelerates skin aging in Chinese women. *J Dermatol Sci* 2015; **79**: 148–154.
42 Vierkötter A, Hüls A, Yamamoto A *et al*. Extrinsic skin ageing in German, Chinese and Japanese women manifests differently in all three groups depending on ethnic background, age and anatomical site. *J Dermatol Sci* 2016; **83**: 219–225.
43 Lefebvre MA, Pham DM, Boussouira B, Bernard D, Camus C, Nguyen QL. Evaluation of the impact of urban pollution on the quality of skin: a multicentre study in Mexico. *Int J Cosmet Sci* 2015; **37**: 329–338.
44 Peng F, Xue CH, Hwang SK, Li WH, Chen Z, Zhang JZ. Exposure to fine particulate matter associated with senile lentigo in Chinese women: a cross-sectional study. *J Eur Acad Dermatol Venereol* 2017; **31**: 355–360.
45 Flament F, Bourokba N, Nouveau S, Li J, Charbonneau A. A severe chronic outdoor urban pollution alters some facial aging signs in Chinese women. A tale of two cities. *Int J Cosmet Sci* 2018; **40**: 467–481.
46 Grether-Beck S, Marini A, Jaenicke T *et al*. Ambient relevant diesel exhaust particles cause skin hyperpigmentation ex vivo and in vivo in human skin: the Düsseldorf Pollution Patch Test. *J Invest Dermatol* 2018; **135**: S205 (Abstract 1209).
47 Fuks KB, Hüls A, Sugiri D *et al*. Tropospheric ozone and skin aging: Results from two German cohort studies. *Environ Int* 2019; **124**: 139–144.
48 Cecchi L, D'Amato G, Annesi-Maesano I. External exposome and allergic respiratory and skin diseases. *J Allergy Clin Immunol* 2018; **141**: 846–857.
49 Ngoc LTN, Park D, Lee Y, Lee YC. Systematic review and meta-analysis of human skin diseases due to particulate matter. *Int J Environ Res Public Health* 2017; **14**: 1458.
50 Kramer U, Behrendt H. [Air pollution and atopic eczema : systematic review of findings from environmental epidemiological studies]. *Hautarzt* 2019; **70**: 169–184.
51 Hidaka T, Ogawa E, Kobayashi EH *et al*. The aryl hydrocarbon receptor AhR links atopic dermatitis and air pollution via induction of the neurotrophic factor artemin. *Nat Immunol* 2017; **18**: 64–73.
52 Liu W, Pan X, Vierkotter A *et al*. A time-series study of the effect of air pollution on outpatient visits for acne vulgaris in Beijing. *Skin Pharmacol Physiol* 2018; **31**: 107–113.
53 Krutmann J, Moyal D, Liu W *et al*. Pollution and acne: is there a link? *Clin Cosmet Investig Dermatol* 2017; **10**: 199–204.
54 Krutmann J, Liu W, Li L *et al*. Pollution and skin: from epidemiological and mechanistic studies to clinical implications. *J Dermatol Sci* 2014; **76**: 163–168.
55 Dreno B, Bettoli V, Araviiskaia E, Sanchez Viera M, Bouloc A. The influence of exposome on acne. *J Eur Acad Dermatol Venereol* 2018; **32**: 812–819.
56 Hüls A, Sugiri D, Fuks K, Krutmann J, Schikowski T. Lentigine formation in Caucasian women - Interaction between particulate matter and solar UVR. *J Invest Dermatol* 2019; **139**: 974–976.
57 Tang X, Wilson SR, Solomon KR, Shao M, Madronich S. Changes in air quality and tropospheric composition due to depletion of stratospheric ozone and interactions with climate. *Photochem Photobiol Sci* 2011; **10**: 280–291.

58 Schikowski T, Guo Q, Hüls A, Sugiri D, Seite S, Krutmann J. Epidemiological evidence for a negative association between air pollution and basal cell carcinoma. *J Invest Dermatol* 2019; **139**: S30 (Abstract 173).
59 Bao L, Xu A, Tong L *et al*. Activated toxicity of diesel particulate extract by ultraviolet a radiation in mammalian cells: role of singlet oxygen. *Environ Health Perspect* 2009; **117**: 436–441.
60 Ohnuki G, Toyooka T, Ibuki Y. UVB in solar-simulated light causes formation of BaP-photoproducts capable of generating phosphorylated histone H2AX. *Mutat Res* 2010; **702**: 70–77.
61 Soeur J, Belaïdi JP, Chollet C *et al*. Photo-pollution stress in skin: Traces of pollutants (PAH and particulate matter) impair redox homeostasis in keratinocytes exposed to UVA1. *J Dermatol Sci* 2017; **86**: 162–169.
62 Zouboulis CC. The human skin as a hormone target and an endocrine gland. *Hormones (Athens)* 2004; **3**: 9–26.
63 Ju Q, Zouboulis CC, Xia L. Environmental pollution and acne: chloracne. *Dermatoendocrinol* 2009; **1**: 125–128.
64 Ju Q, Zouboulis CC. Endocrine-disrupting chemicals and skin manifestations. *Rev Endocr Metab Disord* 2016; **17**: 449–457.
65 Zouboulis CC, Makrantonaki E, Nikolakis G. When the skin is in the center of interest: an aging issue. *Clin Dermatol* 2019; **37**: 296–305.
66 Makrantonaki E, Vogel K, Fimmel S, Oeff M, Seltmann H, Zouboulis CC. Interplay of IGF-I and 17beta-estradiol at age-specific levels in human sebocytes and fibroblasts in vitro. *Exp Gerontol* 2008; **43**: 939–946.
67 Rudman D, Feller AG, Nagraj HS *et al*. Effects of human growth hormone in men over 60 years old. *N Engl J Med* 1990; **323**: 1–6.
68 Zouboulis CC, Chen WC, Thornton MJ, Qin K, Rosenfield R. Sexual hormones in human skin. *Horm Metab Res* 2007; **39**: 85–95.
69 Fritsch M, Orfanos CE, Zouboulis CC. Sebocytes are the key regulators of androgen homeostasis in human skin. *J Invest Dermatol* 2001; **116**: 793–800.
70 Chen W, Tsai SJ, Sheu HM, Tsai JC, Zouboulis CC. Testosterone synthesized in cultured human SZ95 sebocytes derives mainly from dehydroepiandrosterone. *Exp Dermatol* 2010; **19**: 470–472.
71 Hall G, Phillips TJ. Estrogen and skin: the effects of estrogen, menopause, and hormone replacement therapy on the skin. *J Am Acad Dermatol* 2005; **53**: 555–568; quiz 69–72.
72 Youn CS, Kwon OS, Won CH *et al*. Effect of pregnancy and menopause on facial wrinkling in women. *Acta Derm Venereol* 2003; **83**: 419–424.
73 Zouboulis CC, Baron JM, Bohm M *et al*. Frontiers in sebaceous gland biology and pathology. *Exp Dermatol* 2008; **17**: 542–551.
74 Delattre C, Winstall E, Lessard C *et al*. Proteomic analysis identifies new biomarkers for postmenopausal and dry skin. *Exp Dermatol* 2012; **21**: 205–210.
75 Zouboulis CC, Makrantonaki E. The role of hormones in intrinsic aging. In Gilchrest BA, Krutmann J, eds. Skin Aging. Springer, Berlin Heidelberg, Berlin, Heidelberg 2006: 55–64.
76 Slominski A, Wortsman J, Luger T, Paus R, Solomon S. Corticotropin releasing hormone and proopiomelanocortin involvement in the cutaneous response to stress. *Physiol Rev* 2000; **80**: 979–1020.
77 Makrantonaki E, Schonknecht P, Hossini AM *et al*. Skin and brain age together: the role of hormones in the ageing process. *Exp Gerontol* 2010; **45**: 801–813.
78 Elewa RM, Abdallah M, Youssef N, Zouboulis CC. Aging-related changes in cutaneous corticotropin-releasing hormone system reflect a defective neuroendocrine-stress response in aging. *Rejuvenation Res* 2012; **15**: 366–373.
79 Zouboulis CC, Picardo M, Ju Q *et al*. Beyond acne: current aspects of sebaceous gland biology and function. *Rev Endocr Metab Disord* 2016; **17**: 319–334.
80 Zouboulis CC. *Propionibacterium acnes* and sebaceous lipogenesis: a love-hate relationship? *J Invest Dermatol* 2009; **129**: 2093–2096.
81 Chen W, Liao CY, Hung CL, Lin TK, Sheu HM, Zouboulis CC. Potent corticosteroids inhibit lipogenesis in sebaceous glands. *Dermatology* 2006; **213**: 264–265.
82 Ju Q, Tao T, Hu T, Karadag AS, Al-Khuzaei S, Chen W. Sex hormones and acne. *Clin Dermatol* 2017; **35**: 130–137.
83 Zouboulis CC. Acne as a chronic systemic disease. *Clin Dermatol* 2014; **32**: 389–396.
84 Kligman AM. A personal critique on the state of knowledge of Rosacea. *Dermatology* 2004; **208**: 191–197.
85 Fimmel S, Abdel-Naser MB, Kutzner H, Kligman AM, Zouboulis CC. New aspects of the pathogenesis of rosacea. *Drug Discov Today* 2008; **5**: e103–e111.
86 Zouboulis CC, Seltmann H, Hiroi N *et al*. Corticotropin-releasing hormone: an autocrine hormone that promotes lipogenesis in human sebocytes. *Proc Natl Acad Sci USA* 2002; **99**: 7148–7153.
87 Ni Raghallaigh S, Bender K, Lacey N, Brennan L, Powell FC. The fatty acid profile of the skin surface lipid layer in papulopustular rosacea. *Br J Dermatol* 2012; **166**: 279–287.
88 Dajnoki Z, Beke G, Kapitany A *et al*. Sebaceous gland-rich skin is characterized by TSLP expression and distinct immune surveillance which is disturbed in rosacea. *J Invest Dermatol* 2017; **137**: 1114–1125.
89 Elewa R, Zouboulis CC. Molecular mechanisms of action of topical antiaging compounds. *J Egypt Womens Dermatol Soc* 2014; **11**: 73–78.
90 Sator PG, Sator MO, Schmidt JB *et al*. A prospective, randomized, double-blind, placebo-controlled study on the influence of a hormone replacement therapy on skin aging in postmenopausal women. *Climacteric* 2007; **10**: 320–334.
91 Rittie L, Kang S, Voorhees JJ, Fisher GJ. Induction of collagen by estradiol: difference between sun-protected and photodamaged human skin in vivo. *Arch Dermatol* 2008; **144**: 1129–1140.
92 Owen CM, Pal L, Mumford SL *et al*. Effects of hormones on skin wrinkles and rigidity vary by race/ethnicity: four-year follow-up from the ancillary skin study of the Kronos Early Estrogen Prevention Study. *Fertil Steril* 2016; **106**: 1170–1175.e3.
93 Lobo RA. Hormone-replacement therapy: current thinking. *Nat Rev Endocrinol* 2017; **13**: 220–231.
94 Gagliano-Juca T, Basaria S. Testosterone replacement therapy and cardiovascular risk. *Nat Rev Cardiol* 2019; **16**: 555–574.
95 Nouveau S, Bastien P, Baldo F, de Lacharriere O. Effects of topical DHEA on aging skin: a pilot study. *Maturitas* 2008; **59**: 174–181.
96 Calvo E, Luu-The V, Morissette J *et al*. Pangenomic changes induced by DHEA in the skin of postmenopausal women. *J Steroid Biochem Mol Biol* 2008; **112**: 186–193.
97 El-Alfy M, Deloche C, Azzi L *et al*. Skin responses to topical dehydroepiandrosterone: implications in antiageing treatment? *Br J Dermatol* 2010; **163**: 968–976.
98 Strumia R. Skin signs in anorexia nervosa. *Dermatoendocrinol* 2009; **1**: 268–270.
99 Miller KN, Burhans MS, Clark JP *et al*. Aging and caloric restriction impact adipose tissue, adiponectin, and circulating lipids. *Aging Cell* 2017; **16**: 497–507.
100 Katta R, Kramer MJ. Skin and diet: an update on the role of dietary change as a treatment strategy for skin disease. *Skin Therapy Lett* 2018; **23**: 1–5.
101 Chang YS, Trivedi MK, Jha A, Lin YF, Dimaano L, Garcia-Romero MT. Synbiotics for prevention and treatment of atopic dermatitis: a meta-analysis of randomized clinical trials. *JAMA Pediatr* 2016; **170**: 236–242.
102 Mekic S, Jacobs LC, Hamer MA *et al*. A healthy diet in women is associated with less facial wrinkles in a large Dutch population-based cohort. *J Am Acad Dermatol* 2019; **80**: 1358–1363.e2.
103 Noordam R, Gunn DA, Tomlin CC *et al*. High serum glucose levels are associated with a higher perceived age. *Age (Dordr)* 2013; **35**: 189–195.
104 Fisher GJ, Kang S, Varani J *et al*. Mechanisms of photoaging and chronological skin aging. *Arch Dermatol.* 2002; **138**: 1462–1470.
105 Katta R, Brown DN. Diet and skin cancer: the potential role of dietary antioxidants in nonmelanoma skin cancer prevention. *J Skin Cancer* 2015; **2015**: 893149.

106 Bosch R, Philips N, Suarez-Perez JA *et al*. Mechanisms of photoaging and cutaneous photocarcinogenesis, and photoprotective strategies with phytochemicals. *Antioxidants (Basel)* 2015; **4**: 248–268.

107 Parrado C, Philips N, Gilaberte Y, Juarranz A, Gonzalez S. Oral photoprotection: effective agents and potential candidates. *Front Med (Lausanne)* 2018; **5**: 188.

108 Hercberg S, Ezzedine K, Guinot C *et al*. Antioxidant supplementation increases the risk of skin cancers in women but not in men. *J Nutr* 2007; **137**: 2098–2105.

109 Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr* 2014; **17**: 1689–1696.

110 Yadav VR, Prasad S, Sung B, Aggarwal BB. The role of chalcones in suppression of NF-kappaB-mediated inflammation and cancer. *Int Immunopharmacol* 2011; **11**: 295–309.

111 Thring TS, Hili P, Naughton DP. Anti-collagenase, anti-elastase and anti-oxidant activities of extracts from 21 plants. *BMC Complement Altern Med* 2009; **9**: 27.

112 Lim H, Kim HP. Inhibition of mammalian collagenase, matrix metalloproteinase-1, by naturally-occurring flavonoids. *Planta Med* 2007; **73**: 1267–1274.

113 Zeevi D, Korem T, Zmora N *et al*. Personalized nutrition by prediction of glycemic responses. *Cell* 2015; **163**: 1079–1094.

114 Uribarri J, Woodruff S, Goodman S *et al*. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc* 2010; **110**: 911–916.e12.

115 Chen AC, Martin AJ, Choy B *et al*. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. *N Engl J Med* 2015; **373**: 1618–1626.

116 Melnik BC. Linking diet to acne metabolomics, inflammation, and comedogenesis: an update. *Clin Cosmet Investig Dermatol* 2015; **8**: 371–388.

117 Smith RN, Mann NJ, Braue A, Makelainen H, Varigos GA. The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. *J Am Acad Dermatol* 2007; **57**: 247–256.

118 Kwon HH, Yoon JY, Hong JS, Jung JY, Park MS, Suh DH. Clinical and histological effect of a low glycaemic load diet in treatment of acne vulgaris in Korean patients: a randomized, controlled trial. *Acta Derm Venereol* 2012; **92**: 241–246.

119 National Rosacea Society. Hot Sauce, Wine and Tomatoes Cause Flare-ups, Survey Finds 2005. URL https://www.rosacea.org/rosacea-review/2005/fall/hot-sauce-wine-and-tomatoes-cause-flare-ups-survey-finds (last accessed: 01 March 2020).

120 Weiss E, Katta R. Diet and rosacea: the role of dietary change in the management of rosacea. *Dermatol Pract Concept* 2017; **7**: 31–37.

121 Takeshita J, Grewal S, Langan SM *et al*. Psoriasis and comorbid diseases: epidemiology. *J Am Acad Dermatol* 2017; **76**: 377–390.

122 Ford AR, Siegel M, Bagel J *et al*. Dietary recommendations for adults with psoriasis or psoriatic arthritis from the medical board of the national psoriasis foundation: a systematic review. *JAMA Dermatol* 2018; **154**: 934–950.

123 McCusker MM Grant-Kels JM. Healing fats of the skin: the structural and immunologic roles of the omega-6 and omega-3 fatty acids. *Clin Dermatol.* 2010; **28**: 440–51.

124 World Health Organization. Dioxins and their effects on human health. 2016. Available at: https://www.who.int/news-room/fact-sheets/detail/dioxins-and-their-effects-on-human-health (last accessed 20 September 2019).

125 Albuquerque RG, Tufik S, Andersen ML. Sleep quality implicates in life quality: an analysis about children who suffered burns. *Burns* 2014; **40**: 774–775.

126 Slominski AT, Zmijewski MA, Zbytek B, Tobin DJ, Theoharides TC, Rivier J. Key role of CRF in the skin stress response system. *Endocr Rev* 2013; **34**: 827–884.

127 Hunter HJ, Momen SE, Kleyn CE. The impact of psychosocial stress on healthy skin. *Clin Exp Dermatol* 2015; **40**: 540–546.

128 Kahan V, Andersen ML, Tomimori J, Tufik S. Stress, immunity and skin collagen integrity: evidence from animal models and clinical conditions. *Brain Behav Immun* 2009; **23**: 1089–1095.

129 Kahan V, Andersen ML, Tomimori J, Tufik S. Can poor sleep affect skin integrity? *Med Hypotheses* 2010; **75**: 535–537.

130 Ruiz FS, Andersen ML, Guindalini C, Araujo LP, Lopes JD, Tufik S. Sleep influences the immune response and the rejection process alters sleep pattern: evidence from a skin allograft model in mice. *Brain Behav Immun* 2017; **61**: 274–288.

131 Kahan V, Ribeiro DA, Egydio F *et al*. Is lack of sleep capable of inducing DNA damage in aged skin? *Skin Pharmacol Physiol* 2014; **27**: 127–131.

132 Oyetakin-White P, Suggs A, Koo B *et al*. Does poor sleep quality affect skin ageing? *Clin Exp Dermatol* 2015; **40**: 17–22.

133 Yagihara F, Lorenzi-Filho G, Santos-Silva R. Patients with OSA are perceived as younger following treatment with CPAP. *Chest* 2019; **156**: 553–561.

134 Holding BC, Sundelin T, Cairns P, Perrett DI, Axelsson J. The effect of sleep deprivation on objective and subjective measures of facial appearance. *J Sleep Res* 2019; **28**: e12860.

135 Eskandari F, Sternberg EM. Neural-immune interactions in health and disease. *Ann N Y Acad Sci* 2002; **966**: 20–27.

136 Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve–an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev* 2000; **52**: 595–638.

137 Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. *Annu Rev Immunol* 2002; **20**: 125–163.

138 Madva EN, Granstein RD. Nerve-derived transmitters including peptides influence cutaneous immunology. *Brain Behav Immun* 2013; **34**: 1–10.

139 Saint-Mezard P, Chavagnac C, Bosset S *et al*. Psychological stress exerts an adjuvant effect on skin dendritic cell functions in vivo. *J Immunol* 2003; **171**: 4073–4080.

140 Rousset L, Halioua B. Stress and psoriasis. *Int J Dermatol* 2018; **57**: 1165–1172.

141 Egeberg A, Khalid U, Gislason GH, Mallbris L, Skov L, Hansen PR. Psoriasis and sleep apnea: a Danish Nationwide Cohort Study. *J Clin Sleep Med* 2016; **12**: 663–671.

142 Hirotsu C, Rydlewski M, Araújo MS, Tufik S, Andersen ML. Sleep loss and cytokines levels in an experimental model of psoriasis. *PLoS One* 2012; **7**: e51183.

143 Hirotsu C, Nogueira H, Albuquerque RG, Tomimori J, Tufik S Andersen ML. The bidirectional interactions between psoriasis and obstructive sleep apnea. *Int J Dermatol* 2015; **54**: 1352–1358.

144 Poli F, Dreno B, Verschoore M. An epidemiological study of acne in female adults: results of a survey conducted in France. *J Eur Acad Dermatol Venereol* 2001; **15**: 541–545.

145 Suh DH, Kim BY, Min SU *et al*. A multicenter epidemiological study of acne vulgaris in Korea. *Int J Dermatol* 2011; **50**: 673–681.

146 Albuquerque RG, Rocha MA, Bagatin E, Tufik S, Andersen ML. Could adult female acne be associated with modern life? *Arch Dermatol Res* 2014; **306**: 683–688.

147 Ganceviciene R, Graziene V, Fimmel S, Zouboulis CC. Involvement of the corticotropin-releasing hormone system in the pathogenesis of acne vulgaris. *Br J Dermatol* 2009; **160**: 345–352.

148 Albuquerque RG, da Rocha MA, Hirotsu C *et al*. A randomized comparative trial of a combined oral contraceptive and azelaic acid to assess their effect on sleep quality in adult female acne patients. *Arch Dermatol Res* 2015; **307**: 905–915.

149 Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. *Exp Dermatol* 2017; **26**: 659–667.
150 Iwata M, Ota KT, Duman RS. The inflammasome: Pathways linking psychological stress, depression, and systemic illnesses. *Brain Behav Immun* 2013; **31**: 105–114.
151 Amano H, Negishi I, Akiyama H, Ishikawa O. Psychological stress can trigger atopic dermatitis in NC/Nga mice: an inhibitory effect of corticotropin-releasing factor. *Neuropsychopharmacology* 2008; **33**: 566–573.
152 Kim JE, Cho BK, Cho DH, Park HJ. Expression of hypothalamic-pituitary-adrenal axis in common skin diseases: evidence of its association with stress-related disease activity. *Acta Derm Venereol* 2013; **93**: 387–393.
153 Chang HY, Suh DI, Yang S-I *et al*. Prenatal maternal distress affects atopic dermatitis in offspring mediated by oxidative stress. *J Allergy Clin Immunol* 2016; **138**: 468–475.e5.
154 Silverberg JI. Associations between atopic dermatitis and other disorders. *F1000Research* 2018; **7**: 303.
155 Ahn HJ, Shin MK, Seo JK *et al*. Cross-sectional study of psychiatric comorbidities in patients with atopic dermatitis and nonatopic eczema, urticaria, and psoriasis. *Neuropsychiatr Dis Treat* 2019; **15**: 1469–1478.
156 Mostaghimi L, Hetzel S. Insomnia and other sleep complaints in inflammatory versus noninflammatory skin disorders: an observational case-control study. *Int J Dermatol* 2019; **58**: 976–981.
157 Lotti T, D'Erme AM, Hercogova J. The role of neuropeptides in the control of regional immunity. *Clin Dermatol* 2014; **32**: 633–645.
158 Zhang X, Yu M, Yu W, Weinberg J, Shapiro J, McElwee KJ. Development of alopecia areata is associated with higher central and peripheral hypothalamic–pituitary–adrenal tone in the skin graft induced C3H/HeJ mouse model. *J Invest Dermatol* 2009; **129**: 1527–1538.