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Review article

The skin aging exposome

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ABSTRACT

The term "exposome" describes the totality of exposures to which an individual is subjected from conception to death. It includes both external and internal factors as well as the human body's response to these factors. Current exposome research aims to understand the effects all factors have on specific organs, yet today, the exposome of human skin has not received major attention and a corresponding definition is lacking. This review was compiled with the collaboration of European scientists, specialized in either environmental medicine or skin biology. A comprehensive review of the existing literature was performed using PubMed. The search was restricted to exposome factors and skin aging. Key review papers and all relevant, epidemiological, *in vitro*, *ex vivo* and clinical studies were analyzed to determine the key elements of the exposome influencing skin aging. Here we propose a definition of the skin aging exposome. It is based on a summary of the existing scientific evidence for the role of exposome factors in skin aging. We also identify future research needs which concern knowledge about the interaction of distinct exposomal factors with each other and the resulting net effects on skin aging and suggest some protective measures.

Contents

Abbreviations: AhR, arylhydrocarbon receptor; AGE, advanced glycation end products; ERK, extracellular signal regulated kinases; HSP, Heat Shock Protein; IRR, infrared radiation; JNK1/2, Jun N-terminal kinase; MITF, melanogenesis associated transcription factor; MMP, matrix metalloproteinase; PM, Particulate matter; ROS, Reactive oxygen species; SIRT, Sirtuin; UV, ultraviolet radiation; VL, visible light.

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1. Introduction

In 2005, the American cancer epidemiologist Christopher Wild coined the term "exposome" to describe the totality of exposures to which an individual is subjected from conception to death [1]. He emphasized that for a better understanding of the interplay of the human body with the environment and the subsequent development of human pathologies (as well as non-pathological traits), a comprehensive knowledge of the totality of lifelong environmental (i.e. non-genetic) exposures is needed. The exposome analysis therefore complements the human genome. Several attempts have been made since then by Wild himself as well as others to define the exposome more precisely [2–8]. Although today, no single definition of the exposome exists (and because of differences in specific organs this may never be the case) it is generally agreed that both external and internal factors as well as the response of the human body to these factors all add up to define the exposome. Notably, exposome research aims at understanding the totality of all exposome factors the human body or a specific organ is chronically exposed to and thus, knowledge about the net effect(s) caused by the interaction of different factors with each other as well as their combination on a given target organ is of utmost importance.

Despite the fact that the exposome concept was introduced more than ten years ago, the exposome of human skin has not yet received major attention and a corresponding definition is lacking. This is even more surprising given the fact that (i) skin as a barrier organ is subject to lifelong exposure to a large variety of environmental factors, (ii) that the biological responses of human skin to these threats and thus the development of skin traits is well known to be affected by various internal (genetical and non-genetical) factors and that therefore (iii) research on the skin exposome may be viewed as paradigmatic and contribute to a better understanding of other organs as well.

In this review paper we would like to respond to this challenge by providing a definition of the skin exposome based on the existing knowledge about interactions between the skin and the environment. For this purpose, we here focus on a healthy skin trait, i.e. skin aging. We will provide a comprehensive overview about what is demonstrated so far to be the most important environmental factors relevant for skin aging. In addition, we attempt to define knowledge gaps and thus research needs which we feel are crucial for a better understanding of the skin aging exposome. Lastly, we will attempt to translate our theoretical approach into dermatological practice.

2. Methodology

This paper follows two consensus meetings in March and May 2016 of a board of European scientists, specialized in environmental medicine and/or skin biology. During these meetings, the board defined and analyzed the key elements of skin exposome factors, in view of the existing literature. The authors performed a comprehensive literature search using PubMed, with combinations of the following key words: skin aging; skin damage; skin pigmentation and exposome; sunlight; UV radiation; UVB radiation; UVA radiation; visible light; infrared radiation; air pollution; ozone; PM_{10}; $PM_{2.5}$; pollutants; nitrogen dioxide; tobacco; stress; physical activity; nutrition; diet; alcohol; antioxidants; cosmetics; skin care; make-up; cosmetic procedures; heat; cold; climate; water; lack of sleep. All relevant review papers including epidemiological; *in vitro*; *ex vivo* and clinical studies were selected.

3. Definition of the skin aging exposome

Based on our consensus meetings, we here define the skin aging exposome as follows:

The skin aging exposome consists of external and internal factors and their interactions, affecting a human individual from conception to death as well as the response of the human body to these factors that lead to biological and clinical signs of skin aging (Fig. 1).

Specifically, we propose that environmental factors which are part of the skin aging exposome fall into the following major categories: (i) sun radiations: ultraviolet radiation, visible light and infrared radiation, (ii) air pollution, (iii) tobacco smoke, (iv) nutrition, (v) a number of less well studied, miscellaneous factors, as well as (vi) cosmetic products.

In the following paragraphs we describe for each skin aging exposome factor the key evidence our conclusions are based on. We next discuss what is known about the interaction of these

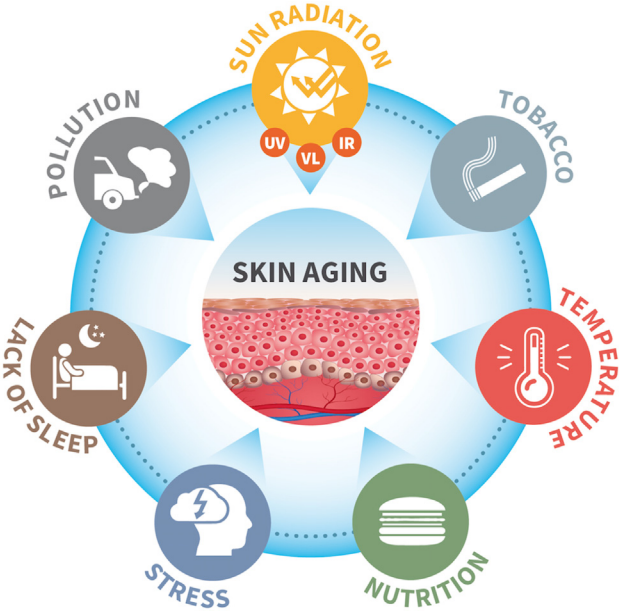

Fig. 1. These Exposome factors have been identified to potentiate skin aging. Exposure to sun, pollution and tobacco are now well known to trigger molecular processes that damage the skin structure, leading to the aged skin appearance. Other, less well studied factors are recognised as potentiators for skin aging. These factors have been shown to act either separately or by interacting with each other and potentiating the process.

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factors (i) with each other and (ii) with internal genetic and non-genetic factors, both in the context of skin aging.

3.1. Solar radiation

Albert Kligman first suggested in 1969 that apart from intrinsic aging factors, sun exposure causes skin damage and aging [9]. More recently, two epidemiological studies, one in Europe [10] and another in China [11] provided significant data to support the relationship between skin aging and sun exposure in two populations of different ethnic backgrounds. In Caucasians, of any age, prevalence of pigmentation disorders is strongly linked to sun exposure, which is not the case for facial ptosis. In Chinese individuals there is also impact of sun exposure with significant influence on many facial aging signs [12].

Sunlight, or the solar spectrum is composed of electromagnetic rays of different wavelengths, ranging from short wavelength, high energy, ultraviolet radiation (UVR) rays to visible light (VL) and to long wavelength, low energy, infrared radiation (IRR) rays (Fig. 2). Most of the solar spectrum reaches the skin. Ultraviolet radiation accounts for 5% of the total solar spectrum and is divided into three groups, in order of shortest to longest wavelength; UVC (100–280 nm) that does not reach the skin, as it is filtered by atmospheric ozone, UVB (280–315 nm), UVA (315–400 nm). The latter accounts for most of the UV radiation that penetrates the skin.

Visible light (400–740 nm) accounts for 50% of the total solar spectrum.

Infrared radiation represents the remaining 45%. IRR is divided into three groups according to wavelength; IRA (740–1400 nm), IRB (1400–3000 nm) and IRC (3000 nm–1 mm). IRB and IRC do not penetrate the skin very deeply but IRA, which represents 30% of IRR does.

UVR, VL and IRR are therefore present in different amounts, have different energy values and penetrate to different skin levels [13].

UVB radiation, is the most energetic but only penetrates the superficial skin layers, down to the epidermal basal layer. UVA radiation is subdivided in UVA_2 (315–340 nm) and UVA_1 (340–400 nm) and is less energetic, but is present in larger amounts. Most particularly, for UVA_1 penetrates deeper into the skin reaching the dermis. VL penetrates deeply into the skin and about 20% reaches the hypodermis. Lastly, 65% of IRA reaches the dermis and 10% the hypodermis.

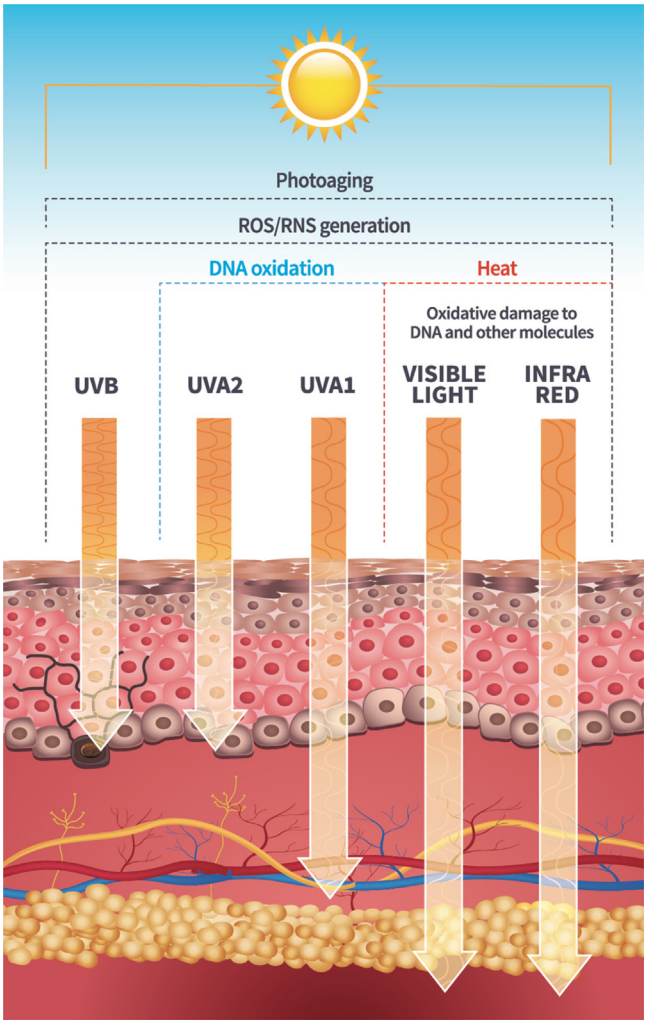

Fig. 2. The solar spectrum is composed of various wavelengths, which penetrate into skin at different levels. The longer the wavelength the deeper the rays penetrate the skin. Each wavelength has both different and overlapping effects. UV = Ultraviolet radiation, ROS = Reactive oxygen species, RNS = reactive nitrogen species. Adapted from E. Dupont, J. Gomez, D. Bilodeau, Beyond UV radiation: a skin under challenge, Int. J. Cosmet. Sci. 35(3) (2013) 224–232.

3.1.1. UV radiation

The role of ultraviolet (UV) radiation in skin aging is well established and the term photoaging has been coined to emphasize this cause and effect relationship. In fact, numerous studies have been conducted during the last few decades to analyze the underlying mechanisms, and based on this knowledge, developed strategies to prevent or at least delay photoaging of human skin. In this regard, UV radiation may be considered as one of the best studied environmental factors contributing to the exposome of skin aging. Several state-of-the art monographs and review articles describing these research efforts are available. Rather than providing another review as part of this manuscript, which for space limitations can only be incomplete, we here would like to highlight a number of key findings which we believe to be of direct importance for our understanding of the exposome of skin aging. Accordingly, we would like to emphasize:

i) that photoaging affects all three compartments of the skin, i.e. the epidermis, dermis and hypodermis,
ii) that changes in the dermal compartment appear to be primary in nature, whereas changes in the epidermis are often secondary, i.e. aged fibroblasts propagate epidermal aging by paracrine mechanisms,
iii) that all UV wavelengths, i.e. UVB, UVA2 and UVA1 radiation contribute to photoaging of human skin,
iv) that the susceptibility toward photoaging is strongly influenced by endogenous protection systems present in human skin such as skin pigmentation, DNA repair, antioxidant defense etc., which may differ between different ethnic groups, age groups and because of genetic differences within these groups,
v) that both acute stress responses (such as upregulation of extracellular matrix degrading enzymes, proinflammatory cytokines etc.) and chronic damage responses, which are caused by the accumulation of macromolecular damage in non-proliferating skin cells (such as mitochondrial DNA damage, oxidized proteins etc.) drive the skin aging process,
vi) that photoaging of human skin mainly results from daily exposure to non-extreme, low doses, which does not cause any visible changes at times of exposure while leading to biological changes and that UVA rays and in particular, long wavelength UVA1 is a major contributor,

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vii) and that evidence is high that regular use of sunscreens can delay photoaging of human skin.

For further details on the scientific evidence these conclusions are based on we would like to refer to the following state-of-art review papers which we consider to be representative for the field [13–19].

3.1.2. Visible and IR light

Visible light (400–740 nm) and IR radiation have long been considered to minimally impact the skin, apart from the heat sensation provided by IR radiation. VL and IR were first reported to induce the production of matrix degrading enzymes such as MMP-1 and MMP-9, and decrease collagen production [20,21]. Interestingly, applying topical anti-oxidants can prevent MMP-1 production. In some studies, the IR radiation doses used could be criticized for exceeding the physiological doses the skin usually receives when an individual is exposed to the sun. Nevertheless, similar MMP-1 production has been further reported using low and repetitive IR doses. Thus, regular exposure to IRA could be more important than expected in premature skin aging [22]. Most importantly, some recent work shows that visible light and particularly infrared light, from natural sunlight can induce MMP-1 expression in exposed skin. In this study, significant MMP-1 upregulation was observed after exposure to natural sunlight even after the UV radiation was filtered out, indicating that both visible light and infrared radiation contribute to MMP-1 expression. Interestingly, the IR response may be partially mediated by heat because MMP-1 upregulation was observed even after exposure to natural sunlight through black clothing to filter out UV, visible and infrared radiation [23]. Similarly, ROS, MMP-1 and IL1 were also reported to be induced after exposure to VL and prevented by using anti-oxidants [24]. VL wavelengths range from violet (400 nm) to profound red (740 nm). Although many studies used the total VL spectrum, growing evidence shows that the different VL wavelengths have specific photobiological impacts on the skin. At a cellular level, keratinocyte and endothelial cell proliferation under visible and IR light, showed that red light (632 and 648 nm) and IRA (850 and 940 nm) have no impact while blue light (412, 419, 426 nm) decreases proliferation and promotes keratinocyte differentiation [25]. Similar results were reported in fibroblasts showing that varying VL and IR wavelengths modulate their gene expression profile differently [26]. Recent *in vivo* data demonstrated that blue light induces radical species production in the skin, using an indirect measure of carotenoid depletion assessed with resonance Raman spectroscopy [27]. More interestingly, direct free radical production was recently measured using EPR spectrophotometry *in vivo* [28]. Importantly, over the time, radical species cumulate, and was measured during UV (325–380 nm), VL and IR irradiation with a maximum production *in vivo* compared to *ex vivo*. This study also revealed that some stratum corneum lipids are modulated after this exposure. After UVR the ceramide subclass [AP2] decreased and the ceramide subclass [NP2], sodium cholesteryl sulfate (SCS) and squalene (SQ) increased. Conversely, after VL and IR irradiations, ceramide [AP2] and SCS increased and SQ significantly decreased.

Although the impact of UVR on skin pigmentation has been known for decades, there is now growing evidence that VL also modulates skin pigmentation. More recently, comparing irradiation of the dorsal skin of healthy volunteers with increasing doses of VL to UVA1 showed that VL is able to induce a marked pigmentation that lasts longer than UVA1 [29]. Interestingly, this level of pigmentation was only observed in darker skinned individuals. Furthermore, the propigmenting properties of blue-violet light (415 nm) were compared to red light (630 nm) on dorsal skin of individuals with type III and IV skin types. The study clearly demonstrated that the blue-violet light induces a marked and prolonged dose-related pigmentation at physiological doses whereas the red light does not induce any pigmentation. Of note, this short VL wavelength-induced pigmentation seems to involve different biological pathways as UVB-induced pigmentation and is not related to the production of radical species [30].

These studies demonstrate that both VL and IRA impact the skin at physiological doses. They induce dermal matrix degradation, modify stratum corneum lipid composition and modulate skin pigmentation. Unsurprisingly, they also show that different wavelengths have specific and sometimes opposite effects on the skin which require further investigation.

3.2. Air pollution

Pollution is a contamination of either the indoor or outdoor environment by any chemical, physical or biological agent. The Environmental Protection Agency (EPA) of the USA classifies pollutants into six categories; lead (metal & industrial processing plants), particulate matter (soot, exhaust, industry), nitrogen oxide (car exhaust), sulphur oxide (industrial plants), ozone (ground level). Air pollution is composed of two main types of primary pollutants; particulate matter (PM), which are commonly referred to as fine ($PM_{2.5,}$ PM_{10}) or coarse particles, and gases ($O_{3,}$ CO_2, CO, SO_2, NO_2) or volatile organic compounds. Small particles are typically produced by combustion and the larger ones by mechanical processes that create and then suspend dust particles in the wind. However, under certain atmospheric conditions, secondary pollutants such as ozone and peroxyacetyl nitrates form from photochemical reactions between the primary pollutants, heat and UV radiation. These pollutants stay low in the atmosphere (troposphere) and settle over both urban and rural areas forming what is typically known as smog.

A relationship between air pollution and skin aging was first shown in the SALIA study, an epidemiological study of elderly Caucasian women, which indicated that exposure to traffic related PM contributes to skin aging [10]. Further cross-sectional studies were then performed in China where rural and urban pollution is particularly present. This provided further epidemiological evidence for skin aging related to contact with fossil fuel [11].

A correlation was also found between NO_2 and pigment spot formation in women over 50 years of age in Germany [10]. These results were supported with further data in the Han Chinese population. An increase in 10 $\mu g/m^3$ NO_2 was associated with 25% more pigment spots on the cheeks in German women, and 24% in Chinese women [31].

A very recent study indicates that exposure to increased ground levels of ozone may be associated with wrinkle formation in the face [32]. This epidemiological evidence puts into context some earlier work that indicates the possible mechanism of action of ozone on the skin. Regular contact with ozone depletes antioxidants from the stratum corneum [33]. Ozone also increases lipid peroxidation and protein oxidation in mouse skin [19,34,35].

In vitro studies have shown that ozone activates the arylhydrocarbon receptor (AhR) in cultured keratinocytes, thus providing a potential mechanism [36]. AhR activation is most likely also involved in PM-induced skin aging. Accordingly, soot, a mixture of carbon particles and organic compounds such as polyaromatic hydrocarbons which can easily penetrate human skin and activate the AhR. Also, genetic studies indicate that significant gene-environment interactions for genetic variants of the AhR pathway exist and that women with a high genetic risk score developed 52% (95% CI: 14–104%) more lentigines on the cheeks after an increase of 4.45 in $PM_{2.5}$ [37].

In conclusion there is now good epidemiological evidence that exposure to traffic-related air pollution including PM, NO_2 and

ground level ozone is associated with pigment spot and wrinkle formation in Caucasians and East Asians and preliminary evidence suggests that at least some of these effects may be mediated via AhR signaling in human skin.

3.3. Tobacco smoking

The relationship between cigarette smoking and skin aging is supported with epidemiological studies and *in vitro* mechanistic evidence. Smoker's skin has been characterised by prominent facial wrinkling particularly around the mouth and upper lip and eyes [38–40]. Heavy smokers were found to have hyperpigmentation of the oral mucosa, called "smoker's melanosis"[41]. Facial pigmentation changes may also occur. Epidemiological evidence exists to indicate female Japanese smokers have darker skin color compared with non smoker [42]. Smoking alters skin hue and radiance, which has been shown to improve with smoking cessation [43]. Twin studies have associated smoking with increased wrinkles, tissue laxity and pigmentary changes in humans. One twin study estimated that, 10 years of smoking corresponded to a difference of appearance of roughly $2^1/_2$ years older [44].

One inhalation from a cigarette contains more than 3,800 different harmful, chemical substances notably nicotine, carbon monoxide, tar, formaldehyde, cyanhydric acid, ammonia, mercury, lead and cadmium. One immediate effect of smoke inhalation is reduced blood flow in the microcirculation with a maximum effect after the first two minutes of consumption, regardless of nicotine concentration contained [45–47]. The N-Nitrosonornicotine found in high levels in tobacco and cigarette smoke contributes to a decrease in the fibroblast migration necessary for wound healing [48]. Cigarette smoke extract impairs fibroblast growth and proliferation and leads to features similar to those seen in senescent fibroblasts. Oxidative stress injury and inhibition of antioxidant defense activity may be involved in this aging process induced by cigarette smoke [49].

MMP1 mRNA is increased in smoker versus non-smoker skin [50]. Recent molecular and cellular studies show that the accelerated aging process is caused by extracellular matrix breakdown following induction of MMP1 expression by the AhR pathway activation [51,52]. Additionally, cigarette smoke modifies melanocyte activity. Smoke extract significantly increases the MITF (melanogenesis associated transcription factor) expression in a dose-dependent manner, leading to more melanin production in melanocytes via AhR-mediated mechanisms [53]. Cigarette smoke and UVA exposure have been shown to cause wrinkle formation *in vivo* and to induce fibroblast MMP1 expression *in vitro* independently of each other [54].

Cigarette smoke alters biological processes in the skin promoting skin aging. However, we still do not know what cumulative doses induce these clinical signs, and how much is due to direct skin exposure *versus* systemic exposure following inhalation.

3.4. Nutrition

Cutaneous signs such as dermatitis, cheilite, perleche, alopecia and depigmentation observed during certain nutritional deficiencies, highlight a link between nutrition and skin [55,56]. In addition, dietary factors and nutritional supplements may influence skin aging. A diet rich in anti-oxidants may delay aging effects and twins who avoid excessive alcohol intake have a younger perceived age [44]. In an epidemiological study higher vitamin C intake was associated with a lower likelihood of wrinkled appearance, while higher fat and carbohydrate intake were associated with higher likelihood of wrinkled appearance [57]. Another study investigated Anglo-celtic, Greek and Swedish people living either in Australia or their native country. A high intake of vegetables, olive oil, and legumes appeared to be protective against cutaneous actinic damage; a high intake of meat, dairy and butter appeared to be adverse [58].

In a cross-sectional survey conducted in 131 healthy Japanese females, a significant correlation was found between coffee consumption and a decrease in pigmented scores but not in wrinkling scores [59]. However, in two other studies in a Mediterranean population, no correlation was found between coffee consumption and wrinkling or solar elastosis; pigmentation was not evaluated [60,61].

Consuming too much sugar is assumed to cause wrinkles [62]. At blame is a natural process that's known as glycation, in which the sugar in the bloodstream binds to proteins to form harmful new molecules called advanced glycation end products (AGEs). The more sugar consumed, the more AGEs developed and the more glycation occurs (Maillard reaction). In the skin, advanced glycation end product (AGE) deposits have been observed in fibronectin, laminin, elastin and collagen. Glycation arises in the dermis after 35 years of age and UV exposure increases cross-linking in the skin. Endogenous glycation occurs when consumed sugar products bind to protein and lipids. Exogenous glycation occurs when food containing AGE formed at high temperatures by roasting, grilling or frying is ingested. Food-derived AGE produced by grilling roasting and frying can induce inflammation and oxidation.

Vitamins, flavonoids, carotenoids and tocopherols have been reported to have antioxidant properties and are therefore used in oral supplements with the aim of prolonging youthful skin appearance [63]. However clinical data demonstrating a visible effect are missing [64]. Therefore the balance between (ROS) and anti-oxidants, for each particular physiological or pathological condition needs to be understood as well as whether antioxidants should be acquired from the diet or nutritional supplements [65].

It is worth noting that beta-carotene (30 mg) and retinyl palmitate (25 000 UI) taken by subjects over a long period of time have been associated with an increased incidence of lung cancer (28%), increased incidence of death (17%) and a higher rate of mortality due to cardiovascular disease compared to the placebo group [66]. Furthermore, in the SU.VI.MAX study, women taking an oral daily capsule of antioxidants (120 mg vitamin C, 30 mg vitamin E, 6 mg beta-carotene, 100 μg selenium, and 20 mg zinc) had a higher incidence of melanoma [67]. The best strategy to achieve a proper ROS/anti-oxidant balance is to consume fruits and vegetables. Supplementation is a strategy only in case of deficiency.

Together these studies provide compelling evidence that nutrition is an exposomal factor relevant for skin aging. The exact extent to which nutrition contributes to skin aging is currently not known. In this regard, it has been estimated that nutrition may account for up to 30% of wrinkle formation in Japanese women [68].

3.5. Miscellaneous

3.5.1. Stress

There is clinical evidence that stress affects skin integrity but there is no direct evidence to show that stress exacerbates skin aging, and this relationship has yet to be clearly demonstrated. Chronic psychological stress stimulates the autonomic nervous system, renin-angiotensin system, and the hypothalamic-pituitary-adrenal axis. This prolonged activation can result in chronic immune dysfunction, increased ROS production, and DNA damage, which are known contributors to skin aging, although the underlying mechanisms have not yet been clearly defined [69].

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Feedback mechanisms and crosstalk between the brain and the skin, have also been found and pro-inflammatory cytokines and neurogenic inflammatory pathways participate in mediating these responses [70]. The by-products of these systems (like cortisol, catecholamines and neuropeptides) can have an impact on the immune system [70]. Even though all skin disorders can be exacerbated by stress, there is a lack of conclusive evidence directly linking psychological stress to skin aging, the underlying mechanisms being ill defined.

Lastly, there is some data to support that stress induces a decline in epidermal permeability and a deterioration in barrier disruption and recovery [71–74].

3.5.2. Sleep deprivation

The impact of sleep deprivation is now recognised to be associated with an increased risk for many chronic diseases such as hypertension, diabetes mellitus, and obesity, cardiovascular disease, depression and even cancer, and several that also increase mortality risk [75]. In skin, restricted sleep has been shown to affect the physical (or aesthetic) facial appearance. One experimental study found subjects with disturbed sleep appeared markedly less healthy, less attractive and more tired with changes in several skin color parameters [76]. Another experimental study found that sleep deprivation affects features relating to the eyes, mouth, and skin. The investigators reported observing hanging eyelids, red, swollen eyes, dark circles under the eyes, paler skin, more wrinkles/fine lines, and droopy corners of the mouth [77]. In terms of skin aging, a cross-sectional study of 60 women, found that those who slept less than 5 h per night exhibited more intrinsic signs of aging, as indicated by the SCINEXA score [78].

A reduced epidermal permeability barrier function was observed during periods of psychological stress due to lack of sleep [79].

3.5.3. Effects of temperature

Normal skin temperature is roughly 33 °C and is a function of ambient temperature [80]. According to J.H. Chung, heat is an environmental factor that may contribute to skin aging. Heat is generated as a consequence of IRR during sun exposure and leads to an increase in skin temperature. The temperature of human skin can increase to more than 40 °C under direct IRR due to the conversion of IR into heat. Acute heat shock in human skin stimulates new vessel formation, recruits inflammatory cells, and causes oxidative DNA damage [81–83].

Chen showed that heat exposure contributes to the accumulation of elastotic material in skin. An *in vivo* study on buttock skin, exposed to heating pads at 43 °C for 90 min showed increased tropoelastin expression in the epidermis and dermis, increased MMP-12 expression in the dermis and, modulation of fibrillin-1 expression increased in the epidermis and decreased in the dermis [84,85].

Severe skin aging has been observed on baker's arms, possibly due to frequent exposure to the hot ovens and on facial skin of glass blowers. For J.Y. Seo and J.H. Chung, heat is an environmental factor that contributes to skin aging, which could be referred to as thermal skin aging [86]. The role of heat in inducing skin aging has also been supported by evidence mentioned previously, that MMP-1 is up regulated after exposure to natural sunlight through black clothing that filtered out UV, visible and infrared radiation, allowing only heat to act on the skin. There is no evidence in the literature for the effect of cold temperatures on skin aging.

3.5.4. Cosmetics

Cosmetic product use has been increasing in recent years. Cosmetics are made to embellish, beautify and improve skin appearance. They are part of the exposome but differ from previously mentioned environmental factors because they are used voluntarily to reduce or prevent skin aging. Indeed, several ingredients have demonstrated their ability to prevent or correct aging signs in randomised controlled trials.

By definition, cosmetic use needs to be safe. The safety approach can be implemented in four stages.

The first stage of the safety evaluation of a product begins with an in-depth knowledge of the raw materials that should be clearly defined with respect to their composition, quality, toxicological, clinical and cosmetic safety data. In particular, the substances used in cosmetics should have a safety assessment verifying that, at the concentrations used, they do not have the characteristics of endocrine disruptors as defined by the World Health Organization.

Secondly, a risk assessment of the associated raw materials is performed. This consists of weighing the intrinsic hazard of each raw material according to how the product is used (whether rinsed off or not after use or applied to the whole body or to just a small area) and thus the nature of the exposure to the human body. The weighting factors also include the frequency of product use. A maximum concentration for use of each raw material is then determined. The concentrations in the finished product should be at least 100 times lower than the no-effect dose.

Thirdly, finished product safety is confirmed under the normal or foreseeable conditions of use to detect the smallest objective sign or discomfort for the future user. If necessary, products are subjected to complementary *in vitro* safety tests and clinical trials conducted on healthy volunteers constituting particular groups such as sensitive skin.

Lastly, once marketed, the product must be monitored by cosmetovigilance procedures. Sometimes a product is modified in response to these reports from consumers and health professionals.

It should be noted that so called "traditional" cosmetics or cosmetics made without such strict rules can be harmful to human skin and thus contribute in a negative to way to the skin exposome [87].

4. Towards an understanding of the totality of exposome factors

As mentioned in the introductory paragraph, an integral part of the exposome concept is the biological impact of the totality of all factors which form the exposome. Historically, however, influencing factors have thus far been studied separately and interactions between distinct factors and the resulting biological consequences for the human body are therefore poorly understood. In this regard, skin aging is a prime example. It is now well established that chronic exposure to natural sunlight is of utmost importance for skin aging. It is without doubt that significant progress has been made in understanding the underlying molecular and cellular mechanisms [14]. These studies, however, have almost exclusively analyzed each wavelength range, i.e. UVB or UVA or visible light or IRA radiation-induced effects on human skin, separately. Given that human skin is naturally exposed to all these wavelengths simultaneously, as part of natural sunlight, it is conceivable to assume that interactions may exist between the different responses elicited by each wavelength range. In support of this concept is work by Schieke et al., who were first to demonstrate a molecular crosstalk between UVA and UVB signaling in human epidermal keratinocytes [88]. Accordingly, UVA radiation alone was found to cause a modest and transient ERK1/2 activation 15–30 min after exposure, whereas UVB irradiation caused a strong and immediate ERK1/2 phosphorylation that lasted for up to 1 h. Only minor activation of p38 and JNK1/2 (Jun N-terminal kinase) was detected after both UVA and UVB irradiation. A different pattern was observed, if keratinocytes were sequentially exposed, i.e. first to UVA followed immediately by UVB exposure. In this

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case, the UVB-induced strong phosphorylation of ERK1/2 was prevented, but instead p38 and JNK phosphorylation were enhanced. Of note, this activation pattern was also observed, if the sequence was altered, i.e. if keratinocytes were first irradiated with UVB and then immediately thereafter with UVA. Combined, these results strongly indicate that UVA and UVB irradiation cause distinct stress responses in keratinocytes and that sequentially eliciting these two stress responses causes a third response, that is different from either alone and cannot be explained by a simple addition of effects. The authors therefore concluded that the molecular crosstalk of UVA and UVB irradiation which they had observed at the level of MAPK signaling represents an evolutionary conserved signaling pathway, which may have developed as an elaborate molecular defense strategy of human skin cells to respond to solar radiation-induced stress in a way which goes beyond a mere additive effect of its single components, i.e. in this case UVA and UVB. Indeed, there is evidence in the literature, that signaling crosstalk may also occur for UVB and IRA radiation, although in this case the response even differs if the sequence of irradiations is being changed from first IRA, then UVB to first UVB, then IRA [89]. Additionally, evidence also suggests that red light interferes in UVA-induced photoaging by acting on different signaling transduction pathways. Red light irradiation decreased the expression of senescence-associated β-galactosidase, upregulated SIRT1 expression and decreased matrix metalloproteinase MMP-1 in human fibroblasts exposed to UVA *in vitro* [90].

These examples emphasize the need for a more detailed analysis of the relative contribution of each wavelength to the net biological effect, which is caused by natural sunlight in human skin cells and which contributes to skin aging. Along the same lines, it is reasonable to assume that crosstalk reactions are not limited to distinct wavelength ranges present in natural sunlight, but will also include other environmental factors which propagate skin aging. Airborne particulate matter and solar radiation for example may not only interact with each other at the level of skin cells, but already further upstream, as exposure of PM to UV radiation is thought to cause “particle aging” through photochemical processes. Similarly, Xia et al. [91] recently provided evidence that UVA radiation of polycyclic aromatic hydrocarbons in air pollution may be a separate metabolic activation pathway and should be investigated further.

We therefore strongly believe that future research should be devoted to a better understanding of the interaction of distinct exposomal factors with each other and the resulting net effects as it concerns skin aging. This information will be key to optimize existing and to develop novel anti-skin aging strategies.

In addition, it is important to keep in mind that although the exposome by definition excludes genetic factors, gene/environment effects are nevertheless an integral part of the skin aging exposome. This is emphasized by the very recent demonstration of gene/environment interactions in air pollution-induced formation of pigment spots on cheeks in elderly Caucasian women, as it is significantly affected by genetic variants in aryl hydrocarbon receptor signaling [31]. Precise knowledge of the role of such gene/environment interactions in environmentally-induced skin aging will help identify susceptible subgroups and provide a scientific basis for the development of customized or even personalized cosmetics to combat skin aging.

5. Translating theoretical approach into dermatological practice

UV radiation, smoking and pollution are the three main factors that have been proven to induce skin aging. There are few studies showing that photoaging is prevented with sunscreen use as chronic exposure is required to see differences [18,92]. A study published in June 2013 was the first to formally follow adult volunteers and evaluate the impact of daily sunscreen use, showing that the daily use of sunscreens retards skin aging in healthy subjects. It was conducted in Australia, at a latitude of 26° south, comparable in latitude to Johannesburg, South Africa, at the same latitude as Texas or Morocco in the northern hemisphere. Subjects, mainly skin types I or II, age 25–55 were randomised to daily or discretionary sunscreen use and assigned to use the same broad-spectrum SPF 15 sunscreen with 2% avobenzone UVA protection. The daily sunscreen group showed no detectable increase in skin aging after 4.5 years as demonstrated with microtopography analysis of a silicone skin cast. Some subjects actually showed an improvement in skin texture over baseline. Skin aging from baseline to the end of the trial was 24% less in the daily sunscreen group than in the discretionary sunscreen group [64]. From this study, we can conclude that using daily sunscreen is more effective than discretionary use to protect against UV-induced skin aging. Starting daily sunscreen use after 25 years of age was shown to still have an impact, which can be seen in as little as 4 years. The authors thus recommend the daily use of a well-

Table 1
General recommendations.

1/General measures
- Avoid smoking.
- Avoid artificial UV exposures (indoor tanning).
- Avoid intentional UV exposure for cosmetic purposes. When outdoors, seek shade whenever possible. Use protective clothing in addition to skin photoprotective care.
- Maintain a healthy life-style, with a diet rich in fruits and vegetables, limited alcohol intake, and enough sleep.

2/Recommendations for daily skin care regimen
A/In the morning:

- Avoid over washing the skin as it may damage the natural skin barrier function. Use a gentle cleanser, avoid soap.
- Use cosmetic products to improve skin barrier function and use cosmetics with topical antioxidants to reduce harmful effects of ozone and IRA on skin aging.
- Use photo protective measures: broad spectrum UVA-UVB sunscreen to block UV radiation and to prevent photo reactive compounds to being produced under UV exposure.
- For darker skinned individuals consider adapted sunscreen to protect the skin from shorter wavelength visible light in addition to well-balanced UVA/UVB protection.

B/In the evening:

- Use rinse-off products (gels, shampoos) to clean off pollution on the skin surface and to reduce particle load.
- Use cosmetic products to improve skin barrier function and to repair aging signs.

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balanced, broad-spectrum sunscreen which contains both UVB and UVA1/UVA and UVB photoprotection with a critical wavelength >370 nm.

Since we do not know whether there are interactions between UVA and UVB, we suggest choosing a photoprotection that filters both in a ratio that resembles the natural exposure with the optimal ratio still to be defined. We suggest adapting photoprotection according to phototype and geographical location. Genetic background and latitude and should be taken into account as the skin is exposed to different levels of UV exposure on a daily basis.

Regarding smoking, we recommend avoiding smoking and to avoid cigarette contaminated environments.

Regarding pollution, the actual benefits of measures like wearing a mask, reducing frying at home, using an air filtration unit and taking supplemental antioxidants remain unproven. Sustained clean air policies remain the most important and efficient solution to reduce air pollution-related health effects. Against skin aging, we suggest the use of rinse-off products to reduce particle load on skin, and of topical products that improve skin barrier function in order to reduce cutaneous pollutant penetration. Daily photoprotection is of further importance as UV radiation may potentiate the deleterious effects of pollutant particles on the skin.

With regards to visible light we suggest dark skin individuals and melasma-prone individuals use adapted photoprotection that blocks blue light to avoid hyperpigmented lesions.

With regards to IRA influencing skin aging, it remains a less well-studied factor today. We suggest using topical antioxidants that could also reduce the harmful effects of ozone on the skin. However today there are still many unanswered questions on what and how much to block [89]. Different approaches can be proposed such as reduce reactive oxygen species with vitamin C, vitamin E, carotenoids, polyphenols or stimulate natural antioxidant pathways.

Nutrition and skin aging still remains a controversial subject. We cannot recommend the intake of non-physiological high dosages of isolated antioxidants. Fruit and vegetables consumption may represent the most healthy and safe method to maintain a balanced diet and youthful appearing skin. Limit alcohol intake and have enough sleep are also probably useful common sense measures.

The recommendations of our working group are summarized in Table 1.

Conflicts of interest

AB, GS, BAB are L'Oréal employees. JK and TP have received consultancy fees from L'Oréal.

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