

# Beyond photoaging: additional factors involved in the process of skin aging

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**Abstract:** Studies assessing the impact of extrinsic factors on skin aging have increased during the last with the increase in life expectancy. Although most of the studies are about the sun radiation impact, many factors should be considered in elderly people, beyond environmental conditions. Lifestyle factors, like diet, sleeping, smoking, should be analyzed carefully, as common age-related conditions (menopause, diabetes, pulmonary diseases, etc.). All these factors could accelerate the natural decline of skin structure and functions, possibly affecting the responses to treatments and drugs. This review demonstrates that growing evidence regarding environmental factors that are associated with lifestyle and comorbidities deserve greater attention from researchers and dermatologists and may require new approaches in the management of skin aging.

**Keywords:** skin aging, oxidative stress, photoaging, pollution, diabetes mellitus, nutrition, glycation, age-related diseases, sleep disorders, chronic stress

## Introduction

Skin aging is the cumulative effect of intrinsic and extrinsic factors. Among extrinsic factors, the effect of solar radiation on skin health is well characterized.<sup>1</sup> Beyond sun damage factors such as smoking and atmospheric pollution have also been studied and considered in extrinsic aging. Studies have shown a clear correlation between these factors and the appearance of melanosis and wrinkles.<sup>2,3</sup> Both of these factors contribute to aging through a common mechanism called oxidative stress that has a negative impact on cellular processes, such as DNA replication. In addition to the ultraviolet (UV) region of solar radiation that contributes to cellular injury, visible radiation has an oxidative effect similar to that of infrared radiation via heat generation.<sup>4</sup>

Additional mechanism to consider is glycation that occurs in common diseases, such as diabetes mellitus, and promotes dermal damage. Glycation also favors oxidation and is implicated in tissue repair disorders.<sup>5</sup> Furthermore, the pathophysiological changes that result during menopause have been thoroughly studied, and it has been found that there exists a correlation between aging and skin changes related to reductions in estrogen levels.<sup>6</sup>

The effects of comorbidities, such as metabolic illnesses common in the elderly, nutritional deficiencies, and the use of drugs such as corticosteroids, and even cancer treatments, should be assessed by dermatologists attending to skin conditions associated with aging.

As life expectancy increases, age-related diseases, lifestyle habits, and environmental factors have a cumulative and synergetic effects on skin aging. Studies assessing the

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impact of extrinsic factors of aging have increased during the last decade, probably because of the medical advancements that have prolonged the lifespan and consequently led to an increase in the number of the elderly. According to the 2015 United Nations World Population Aging Report, the number of individuals aged >60 years and >80 years will double and triple, respectively, by 2050.<sup>7</sup>

In 2005, the epidemiologist Christopher Wild coined the term “exposome” to describe the totality of exposures that an individual is subjected to from conception to death.<sup>8</sup> Later, Krutmann et al<sup>9</sup> published a review article on this topic and defined the exposome for skin aging and proposed the following as the major environmental factors associated: solar radiation (ie, UV, visible, and infrared), atmospheric pollution, and tobacco smoke.

Maintaining the functional and anatomical integrity of the skin is essential. Although vitality is reflected in esthetic characteristics, such as wrinkles, spots, and sagging, the challenge goes beyond maintaining appearance.

Essential functions such as the defensive and repair capabilities of the skin tend to decline and must be preserved in the elderly. During the process of aging, the skin becomes thinner, stiffer, less tense and less flexible, which lowers its protective functions against mechanical injuries.<sup>10</sup>

Transepidermal water loss (a measure of the stratum corneum integrity) seems to be unaltered with chronological aging; however, surface lipid production decreases significantly with age increasing incidence of xerosis, pruritus, and skin irritation in elderly populations.<sup>11</sup>

These alterations may worsen with extrinsic factors that affect the skin structure; not only photodamage or skin pollution but lifestyle factors (emotional stress, smoking, diet, etc.)<sup>12</sup> or even aging-related conditions such as diabetes, menopause or chronic inflammatory diseases.<sup>13,14</sup>

The dermatologic complications that accompany longevity include 1) skin diseases and age-related dysfunctions;<sup>15</sup> 2) changes in the pattern of skin responses to dermatological procedures and treatments, such as healing and reductions in barrier functions;<sup>16-18</sup> and 3) the repercussions of new treatments for skin and systemic diseases that are more common in the elderly.<sup>19,20</sup>

This review highlights conditions beyond photoaging that affect skin aging, the relevance of which increases with longer life expectancy.

## Phototype X photodamage

The mere occurrence of a low Fitzpatrick phototype should be considered a major risk factor for age-related skin damage

because the lower melanin synthesis reduces the first defense against UV rays. Although phototype is a physiological characteristic, intense and early manifestation of a large portion of extrinsic factors predominantly happens in light-skinned individuals.<sup>21</sup>

In addition to having lower melanization, individuals with lower phototypes (1 and 2) have significantly fewer dermal papillae, as observed with confocal microscopy, than those with higher skin phototypes and with darker skin. This phenomenon increases significantly with age, particularly in individuals with light skin.<sup>22</sup> Pheomelanin, which predominates in light-skinned individuals, is synthesized in response to UV stimuli. This synthesis is associated with increased oxidative stress and possibly carcinogenesis.<sup>23</sup>

Similarly, the presence of photodamage, which is clinically characterized by the gradient of color and texture between exposed and covered skin, reveals information about patient environment and habits. In addition to photoaging and photocarcinogenesis, photodamage can lead to dermal repair alterations because it impacts the expression of metalloproteinases.<sup>24</sup>

UV damage can also cause significant changes in some of the mechanical properties of the stratum corneum, reducing its cell cohesion and mechanical integrity; the UV radiation also affects the molecular structure of cell proteins and lipids.<sup>25</sup>

## Environmental factors beyond UV radiation

### Infrared radiation and heat

Infrared thermogenic radiation can reach the dermis (65%) and hypodermis (10%), and its capacity to induce metalloproteinase expression in the dermis is well known along with its oxidative role.<sup>26</sup> Both infrared radiation and heat-induced acute stress increase in the number of mast cells and expression of tryptase. Chronic exposure induces angiogenesis and cellular inflammatory infiltrates and damages the dermal extracellular matrix and protein structures of the dermis, thus promoting the skin aging.<sup>27</sup>

Short exposures of electronic device generated light (EDGL) increase reactive oxygen species (ROS) generation, but the long-term effects associated with repeated exposures of EDGL are still unknown.<sup>28</sup>

In human skin, UV radiation can initiate neutrophilic inflammatory infiltrates. Similarly, infrared radiation and heat can lead to macrophage recruitment.<sup>29</sup> The association between non-melanoma skin cancer and erythema ab igne, a disease typically caused by heat, has been established.<sup>30</sup>

## Pollution

Oxidative damage derived from atmospheric pollution can cause various types of skin damage.<sup>31</sup> This relationship was demonstrated in a study showing that exposure to air pollution in traffic was related to skin aging in light-skinned women.<sup>32</sup> Polycyclic aromatic hydrocarbons are associated with signs of extrinsic aging, pigmentation, and skin cancer. This damage is worsened by solar radiation. UVA combined with environmental pollutants (including cigarette smoke) significantly increases the risk of skin cancer. When ozone exposure precedes UV exposure, there is an enhancement of UV-induced depletion of protective vitamin E from the skin's stratum corneum.<sup>33</sup>

Even in indoor conditions, Ding et al showed that PM<sub>2.5</sub> exposure levels were positively associated with skin aging manifestation. The major mechanism of ambient PM is the generation of ROS. Particles can serve as carriers for organic chemicals and metals that are capable of localizing in mitochondria and generating ROS directly in mitochondria leading to collagen degradation in human skin.<sup>34</sup>

## Lifestyle-related factors

### Smoking

Harmful effects of smoking have been known for decades.<sup>35</sup> Particularly owing to nicotine, smoking negatively affects the dermal microvasculature and hinders the healing process.<sup>36</sup> It also has a toxic effect on keratinocytes and fibroblasts by increasing the expression of metalloproteins and tropoelastin. Furthermore, smoking increases the expression of small proteoglycans and reduces the synthesis of procollagen.<sup>37</sup> The clinical manifestations of these phenomena are pale and wrinkled skin; DNA mutations also result from oxidative effects or direct toxic damage.<sup>38,39</sup>

Smoking is an important independent factor in skin aging, observed in an identical twin study, which concluded that 5-year difference in smoking history is associated with skin changes.<sup>40</sup>

Smoking can accelerate advanced glycation end-products formation and increases their deposition in various tissues, including the skin, similarly to UV radiation.<sup>41</sup>

### Sleep

A clinical study of post-menopausal women showed that those who slept for <5 h/day had higher levels of transepidermal water loss and decreased skin barrier recovery after UV-induced erythema.<sup>42</sup> Even after a single night of sleep deprivation, periocular areas show worsened dark circles probably because of slight edema, which gives a tired or "saddened" appearance.<sup>43</sup> As sleeping is critical for cellular growth and

renovation, poor sleep quality leads to cellular dysfunction due to disruption of the circadian rhythm and therefore results in changes in various tissues, including the skin.<sup>44,45</sup>

A large Japanese study with 10,946 volunteers demonstrated that lifestyle habits such as physical activity, non-smoking, adequate sleep, low mental stress level, eating breakfast, and abstaining from sugary food were each independently associated with lower AGE generation.<sup>46</sup>

### Low-antioxidant diet

Nutritional status is a relevant concern throughout life. In older age, the diet should be considered carefully, because micronutrients are more difficult to obtain in restricted diets.<sup>47</sup> Micronutrients with antioxidant activity are present in various vegetables, and a rich and varied diet including these foods meets antioxidant requirements. However, when oxidative stress is present, antioxidants obtained from the diet and endogenous systems may be insufficient.<sup>48</sup>

Another relevant issue is the greater loss of micronutrients (due to lower absorption) or even lower ingestion that may occur in the elderly. Folic acid, vitamin D, calcium, and vitamin B12 deficiencies are prevalent,<sup>49</sup> and they tend to increase with age, particularly when reduced absorption or decreased ingestion occurs.<sup>50</sup>

A Dutch study correlates Dietary habits with facial wrinkling in women. The authors demonstrated that red meat and snack consuming pattern was associated with more facial wrinkles whereas a fruit dominant consuming pattern was associated with fewer wrinkles.<sup>51</sup>

Higher intake of vegetables and olive oil appeared to protect against actinic damage. In another study of over 4,000 women, patients' skin was analyzed for features of skin aging. After controlling for other factors, a diet reported as high in potassium and vitamins A and C correlated to fewer wrinkles.<sup>52</sup>

### Long, hot baths with harsh soap

Dry skin often occurs in the elderly and tends to worsen in association with hot baths and the use of standard alkaline bar soaps.<sup>53</sup> Even in younger individuals, long and hot baths are associated with skin pH changes and irritation due to the consequent disruptions to the skin barrier, which worsen xerosis.<sup>54</sup>

## Systemic morbidities and drugs

### Diabetes mellitus

Diabetes mellitus is among the most common aging-related comorbidities, and the generation of advanced glycation

end products is intimately related to dermal damage since it changes the properties of collagen types I and IV.<sup>55</sup> Clinically, reductions in flexibility and rigidity and an increase in susceptibility to mechanical stimulation are observed.<sup>56</sup> These changes are not restricted to dermal collagen and affect endothelial collagen as well, with a concomitant loss in wound-healing capability. The effects of increased advanced glycation end products are worsened by the presence of a hyperglycemic diet and smoking.<sup>19</sup> Diabetes is also very common in the elderly and is an important predictive factor in the development of chronic ulcers and the itching associated with skin xerosis.<sup>57</sup>

## Obesity

Obesity is more prevalent in older age groups for various reasons, predominantly lower metabolic rate and reduced physical activity. A hyperglycemic state is common in obesity and is associated with peripheral resistance to insulin and a higher risk of glycation.<sup>58</sup>

One study investigated the association between glucose metabolism and perceived age. Perceived age was assessed using facial photographs, and the mean glycemia and insulin levels were measured in 602 individuals, who were divided into diabetic and nondiabetic groups according to the level of glycemia. A significant correlation was found between the increase in perceived age and glycemia levels in these patients, which demonstrated that elevated glucose levels are associated with older apparent age, even in nondiabetic individuals.<sup>59</sup>

## Menopause

Reduced estrogen levels during menopause affect skin components with estrogen receptors, particularly in epidermal cells and sebaceous glands.<sup>60</sup> By contrast, androgenic hormone levels do not decline significantly during this period. Although the response to this new ratio of sexual hormones is often clinically mistaken for the natural functional decline of the skin, menopause can increase xerosis, changes in texture and capillary density, and dermal atrophy.<sup>61,62</sup>

## Body mass index <18.5

Although research has shown that calorie-restricted diets can improve longevity and reduce comorbidities associated with aging.<sup>63</sup> The risk of protein-caloric malnutrition, which leads to immunosuppression and healing deficiencies, remains relevant.<sup>64,65</sup> On the contrary, no studies have demonstrated that undernutrition or malnutrition, which leads to a body mass index below normal levels, has negative impacts on

the skin senescence process. However, there is evidence suggesting that a lack of macronutrients can be deleterious in this process.<sup>65</sup>

## Acne scarring

Skin with acne scarring has reduced elasticity due to scar fibrosis and shows a worsened appearance of furrows and wrinkles.<sup>66</sup> There are no studies investigating this ailment alone because the treatments for scarred and aged skin can be similar.<sup>67</sup>

## Frequent use of systemic corticosteroids

Increased cortisol levels are associated with vasoconstriction, immunosuppression, changes in wound healing, and increased glycemia. Although these drugs do not have direct effect on skin, however, their chronic use worsens the degenerative process of aging.<sup>68</sup>

## Other chronic clinical conditions

The more common comorbidities of advanced age can have a negative impact on the process of skin aging through various mechanisms and should, therefore, be recognized and studied on a case-by-case basis.<sup>69</sup> For example, there are peculiarities of chronic diseases that have direct effects on the skin. COPD is correlated with chronic skin ulcers and increases the signs of skin aging.<sup>70</sup> Chronic renal insufficiency leads to persistent itching with neural and immune changes in addition to impairing wound-healing response.<sup>71</sup> Rheumatic diseases interfere with dermal microvasculature and collagen synthesis.<sup>72</sup> Although these diseases are prevalent in more advanced age groups, only a few studies have investigated their impact on the skin and their interference with proposed esthetic treatments.<sup>73,74</sup>

## Emotional stress

Chronic emotional stress alters barrier homeostasis, possibly through increases in cortisol levels.<sup>75</sup> A study using animal models of stress reported increases in lipid peroxidation, inflammatory infiltrates, and metalloproteinase levels, thus demonstrating that stress can trigger aging mechanisms.<sup>76</sup> Another study correlated the subjective older appearance with greater stress because of financial difficulties.<sup>77</sup> However, levels of cortisol or other oxidative markers were not measured.

## Other indirect factors

Some factors may be correlated with skin aging because they are implicated in oxidative processes or worsen conditions that are directly related to skin aging.

## Sedentarism X intensive exercises

The benefits of moderate exercise vary and include improved circulation, dermal oxygenation, and reduced glycation indexes.<sup>78,79</sup> However, no clinical study has demonstrated a clear relationship between physical inactivity and skin aging. Conversely, the heavy exercise performed by professional athletes can increase oxidative stress, but there are no clinical studies showing a relationship between degenerative skin processes and intense physical activity.<sup>80</sup>

## Hypoproteic diet

The relationship between skin aging and the ingestion of macronutrients requires further study. Low-protein diets are associated with wound-healing problems, particularly in the elderly; however, few studies have investigated the correlation between low protein ingestion and changes in the pattern of skin element synthesis.<sup>81</sup> A clinical study showed that intake of specific bioactive collagen peptide had positive effects on dermal matrix synthesis, but these results could not be similar to the whole protein.<sup>82</sup>

## Hyperglycemic diet

Due to its greater risk of glycation, a hyperglycemic diet is a predisposing factor for skin aging.<sup>83</sup> It is challenging to study this relationship because obesity and diabetes are associated in most patients.

It is important to consider the possibility that any process that increases oxidative stress can create an imbalance in endogenous systems and deplete physiological reserves. Oxidative damage increases with advanced age because intrinsic aging itself is more oxidative. In addition, the ability of human cells to repair DNA damage decreases over time.<sup>84</sup> Thus, these factors and mechanisms can overlap, increasing the potential for cumulative skin damage.

The Consensus Statement of the Delegates of the 2014 Manchester Summit discusses key issues related to skin aging and health – in particular, the increasing prevalence of dermatosis, including skin cancer, and the importance of awareness and prevention measures. According to the authors, maintaining healthy skin should be one of the foundations of overall health and better quality of life.<sup>85</sup> Therefore, in anticipation of a longer lifespan, it is essential to investigate factors that contribute to aging of the skin. Dermatologists should focus on helping patients to maintain not only skin appearance but also on skin health.

## Conclusion

As life expectancy increases, its related comorbidities require greater attention within the context of skin aging because

wound healing, skin barrier maintenance, and other functions decline with age. Although the major concerns are often esthetic features, such as wrinkles or melanosis, the incidence of skin carcinogenesis also tends to increase in older adults. Environmental factors associated with lifestyle and systemic comorbidities deserve greater attention from dermatologists when managing skin aging in patients. Understanding these factors related to life expectancy and preventing their repercussions on the skin are the new missions of dermatologists.

## Disclosure

The author reports no conflicts of interest in this work.

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