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AIR POLLUTION AND HEALTH (T NAWROT, SECTION EDITOR)

# Air Pollution and Skin Aging

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## Abstract

**Purpose of the Review** The evidence on the role of air pollution on skin aging has increased in recent years. The accumulating evidence is based on both, epidemiological and mechanistic studies. The purpose of this review is to evaluate the recent evidence on the impacts of air pollution on skin aging as well as identify knowledge gaps for future research.

**Recent Findings** Traffic-related air pollution exposure (particulate matter (PM), soot and nitrogen dioxide ($NO_2$)) has been associated with premature skin aging in several independent cohorts. In real life, human skin is additionally exposed to UV radiation, which is known for its effects on premature skin aging. More recent epidemiological findings suggest that (1) associations of PM can be altered by UV radiation with stronger PM associations at lower levels of UV, and (2) there is an association of tropospheric ozone with wrinkle formation, independent of $NO_2$, PM, and UV.

**Summary** The association between traffic-related air pollution and skin aging has been well-established. More recent epidemiological studies focused on the associations with ozone as well as interactions with of ambient air pollution with UV radiation, a research area that is becoming more important with the increase of global warming.

**Keywords** Environmental influences · Ozone · Ultraviolet radiation · Nitrogen oxides · Particulate matter · Soot

## Introduction

Recent evidence indicates that air pollution can not only affect our respiratory and cardiovascular system [1–3] but can also exert negative effects on human skin.

Air pollution is a contamination of either the indoor or outdoor environment by any chemical, physical, or biological agent [4]. Air pollution is currently considered the world's largest single environmental health risk factor [5], and in 2013, the International Agency for Research on Cancer (IRAC) classified outdoor air pollution as carcinogenic to humans [6]. Air pollution is mainly composed of a mixture of components: particulate matter in various sizes ($PM_{10}$, $PM_{2.5}$, or smaller) and gases ($O_3$, $NO_x$, $NO_2$, and $CO_2$). Small particles are typically produced by combustion and the larger ones by mechanical processes. Under certain atmospheric conditions, however, secondary pollutants such as ozone and peroxyacetyl nitrate are additionally produced from photochemical reactions between the primary pollutants (e.g., $NO_2$) and ultraviolet (UV) radiation. These pollutants remain low in the atmosphere (troposphere) and settle both in urban and rural areas, forming so-called smog. In cities, most air pollutants are caused by combustion processes from industry or road traffic. The different emission sources can influence the composition, effect, and size of the particles. In urban areas, additional high $NO_2$ values are added by diesel engines, which can negatively impact air quality.

Aging is accompanied by progressive deterioration of structure and function of all tissues, including visible signs of skin aging. Among all organs, skin is the most visible, and skin aging directly impacts individual self-esteem [7]. This is illustrated best by the fact that the market for cosmetic and medical products devoted to the prevention and treatment of skin aging has 15 billion US$ worth of sales worldwide [8]. Signs of skin aging might further serve as a mirror reflecting internal aging processes of the human body [9, 10] with the peculiarity that skin aging signs are directly visible and can be studied noninvasively.

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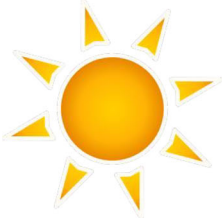
Aging of the skin is influenced by several factors and can be distinguished between extrinsic and intrinsic skin aging. Intrinsic skin aging is the general aging process, determined by the genetic make-up, and occurs over time. Extrinsic aging is the process influenced by environmental factors such as smoking, air pollution, and UV radiation. Each of the skin aging processes is associated with characteristic skin aging signs: The extrinsic skin aging process is characterized by morphological and physiological changes and leads to premature aging of the skin [11]. Prominent signs ar coarse wrinkle formation, pigment spot formation, and solar elastosis. The degree of skin aging varies largely among individuals and ethnic groups [12]. The most prominent environmental factor associated with premature skin aging is UV radiation [13, 14••, 15–17]. However, in recent years, the role of exposure to traffic-related ambient air pollution on premature skin aging has been recognized (Table 1). The association of PM exposure and skin aging has been established in several epidemiological studies [18, 19•] and has been confirmed by mechanistic studies [20–22]. Furthermore, nitrogen dioxide ($NO_2$) exposure, which is a good proxy measure of urban-scale variability in chronic exposures to complex urban air pollution mixtures [23], has been linked to pigment or age spots (lentigo senilis) in two cohorts from Germany and China [22], and ozone exposure has been linked to wrinkle formation in two cohorts from Germany [19•]. Newer studies further suggest that the effects of UV radiation and air pollution are not independent of each other, suggesting that pigment spots are the consequence of an interplay of UV radiation and air pollution [24•].

## Traffic-Related Air Pollution

### Particulate Matter and Soot

Long-term or acute exposure to traffic-related air pollutants can lead to varying degrees of damage to health, ranging from

**Table 1** Epidemiological and mechanistic evidence on the association between air pollution and skin aging (selected publications)

| UV radiation | Traffic-related air pollution | | UV radiation & traffic-related air pollution | | Indoor air pollution |
|---|---|---|---|---|---|
|  |  | |  | |  |
| | **Particulate matter & soot** | **Nitrogen oxides** | **Ozone** | **Interactions** | |
| Association well-established (epidemiological and mechanistic evidence) | Association well-established (epidemiological and mechanistic evidence) | Limited epidemiological & lack of mechanistic evidence | Limited epidemiological evidence, good mechsnistic evidence | Limited epidemiological evidence, good mechsnistic evidence | Limited epidemiological evidence, good mechanistic evidence |
| **A) Epidemiological studies:** | | | | | |
| Bastiaens et al. (2004)<br>Derancourt et al. (2006)<br>Monestier et al. (2006) | Vierkötter et al. (2010)<br>Flament et al. (2018)<br>Peng et al. (2017) | Hüls et al. (2016) | Fuks et al. (2019) | Hüls et al. (2019) | Li et al. (2015)<br>Ding et al. (2017) |
| **B) Mechanistic studies:** | | | | | |
| Salducci et al. (2014)<br>Yamada et al. (2014) | Grether-Beck et al. (2018)<br>Jux et al. (2010)<br>Nakamura et al. (2015)<br>Park et al. (2018) | | Valacchi et al. (2011)<br>Thiele et al. (1997)<br>Fortino et al. (2007) | Bao et al. (2009)<br>Ohnuki et al. (2010)<br>Soeur et al. (2017)<br>Tang et al. (2011) | (see „particulate matter & soot“) |

respiratory diseases to premature death [25, 26]. However, it has also been known for some years that air pollutants cause the skin to age prematurely and lead to pigment spot formation.

The connection between traffic-related air pollution and skin aging was first shown in the SALIA study (Study on the influence of Air pollution on Lung function, Inflammation and Aging), an epidemiological study of older women from the Ruhr area and southern Münsterland. The study showed that exposure to traffic-related particles and soot contribute to premature skin aging [18]. Further cross-sectional studies were then carried out in China [27–29] and Mexico [30], where pollution is particularly bad in urban areas.

Lefebvre et al. compared biochemical and clinical skin parameters in rural vs. urban areas in Mexico [30] as well as in China [28]. The study in Mexico investigated the impact of urban air pollution on biochemical and clinical parameters of the skin in 189 healthy volunteers living in Mexico [30]. The study compared skin parameters from volunteers living in Mexico City with volunteers living in Cuernavaca, a rural town 50 km away from Mexico City. The study in China was conducted on 79 subjects from Xu Jia Hui (a center Shanghainese area), more exposed to pollution, and 80 subjects from Chong Ming, an agricultural region closely located north of Shanghai (< 100 km) and less exposed to pollution, according to official data [28]. Both studies show a significant impact of the pollution upon the skin status, as illustrated by changes in superficial biochemical parameters: The authors observed a decrease of the cutaneous contents of squalene (major lipid component of the thick oily substance on the skin called "sebum") and vitamin E as well as an increase of lactic acid in participants from polluted areas in both studies, which are known biochemical markers of the cellular oxidative status.

In another study, Peng and colleagues [29] found an association between $PM_{2.5}$ and the development of senile lentigines. In this study, exposure to $PM_{2.5}$ was significantly associated with more severe senile lentigo development. Participants from the highly polluted area had 1.48 and 2.80 times higher number of spots on cheeks and back of hands compared to residents from less polluted areas.

All these studies provide epidemiological evidence for skin aging associated with exposure to air pollutants. All studies showed that exposure to particulate matter was associated with the appearance of pigment spots on the forehead and cheek.

Mechanistic investigations showed that a topical exposure of human ex vivo skin models with environmentally relevant, nontoxic concentrations of an internationally established reference standard diesel exhaust mixture increases the pigmentation of the skin depending on time and dose [21]. This tanning effect is based on an increase in the synthesis of melanin in the skin. The increased formation of new melanin is triggered by a reaction in the skin that is caused by oxidative stress, followed by oxidative DNA damage and activation of the p53 signaling pathway in the skin (Gether-Beck S, Krutmann J, unpublished data). In line with the ex vivo findings on the role of oxidative stress, clinical studies show that cosmetic products containing selected antioxidants are very well-suited to reduce or even prevent the pigmentation reaction of the human skin caused by air pollution.

Traffic-related air pollutants (e.g., diesel exhaust gases or fine particles), for which the association with skin aging has been well-established, are rich in polycyclic aromatic hydrocarbons (PAHs). These are formed by incomplete combustion of organic material such as coal or oil. PAHs are lipophilic and are more likely to penetrate the skin barrier. It is also known that ligands of the aryl hydrocarbon receptor (AHR), such as PAHs and dioxin, stimulate melanocyte proliferation and thus skin pigmentation [31]. Thus it is possible that at least some of the effects of traffic-related air pollution on skin aging are mediated by PAHs, which are carried by the particles or soot onto the skin and into follicular structures and can diffuse from there into the skin, reach living cells and contribute to an increased formation of pigment spots by influencing the gene expression pattern of this cell population [20].

### Nitrogen Oxides

An epidemiological study has also found a link between nitrogen dioxide ($NO_2$) exposure and pigmentation in German as well as Han Chinese women over 50 years of age [22]. An increase of 10 μg / $m^3$ $NO_2$ was associated with 25% more pigment spots on the cheeks in German women and 24% in Chinese women [22]. Nitrogen oxides are known to be the best proxy measures of urban-scale variability in chronic exposures to complex urban air pollution mixtures [23]. They are highly correlated with ultrafine particles as well as with black carbon, which are both mainly linked to traffic emissions [23]. Therefore, in the epidemiological study [22], the effects of $NO_2$ could not be differentiated from the effects of particulate matter. As a consequence, mechanistic studies are needed to isolate the effects of $NO_2$ on human skin.

## Indoor Air Pollution

Besides ambient air pollution, indoor air pollution has also been recognized as a risk factor for premature skin aging. According to the Global Burden of Disease, Injuries, and Risk Factors Study 2015, indoor air pollution accounted for about 2.9 million deaths and 85.6 million disability-adjusted life years (DALYs) in 2015 [32]. Indoor air pollution arises from domestic activities of cooking, heating, and lighting, particularly in low and middle income countries (LMICs). Three billion people worldwide are exposed to toxic amounts of indoor air pollution every day because they use solid fuels, a term that includes biomass fuels (derived from plant sources) or coal for combustion [33].

Up to now, only two studies have been conducted on the effects of indoor air pollution on premature skin aging [34, 35].

The first study aimed to assess the association between cooking with solid fuels and signs of skin aging in women from Pingding (northern China, $N = 405$) and Taizhou (southern China, $N = 857$) [34]. The analysis showed that cooking with solid fuels was significantly associated with a 5–8% more severe wrinkle appearance on the face and a 74% increased risk of having fine wrinkles on the back of hands in both studies combined, independent of age and other influences on skin aging.

In a follow-up study from the same group, indoor $PM_{2.5}$ exposure was directly measured in 30 households in Taizhou, China [35]. Based on the directly measured $PM_{2.5}$ exposure and questionnaire data of indoor pollution sources, they built a regression model to predict the $PM_{2.5}$ exposure in larger datasets including an initial examination group ($N = 874$) and a second examination group ($N = 1003$). In this study, indoor $PM_{2.5}$ exposure levels was positively associated with skin aging manifestation, including score of pigment spots on the forehead and wrinkle on upper lip in both examination groups.

## UV Radiation and Traffic-Related Air Pollution

### Ozone

Another gaseous pollutant with adverse effects on human health is tropospheric ozone ($O_3$). $O_3$ is formed in a chain of complex photochemical reactions, requiring the presence of nitrogen oxides, volatile organic compounds, other air pollutants, and solar radiation [36]. Therefore, high levels of ozone are directly linked to warmer temperatures caused by climate change. In a recent publication, Fuks et al. [19•] indicated that exposure to high levels of ground-level ozone ($O_3$) was associated with wrinkle formation in the face in two independent cohorts from Germany. These associations were robust to adjustment for particulate matter and nitrogen dioxide in the two pollutant models.

The epidemiological evidence on ozone and wrinkle formation confirms earlier mechanistic studies. $O_3$ was shown to rapidly oxidize the macromolecules in the skin, such as lipids and proteins, producing radical species, such as hydroxyl radical, and triggering oxidative stress [37, 38]. Over two decades ago, Thiele et al. (1997) reported that short-term $O_3$ exposure was effective in depleting antioxidants from the stratum corneum in the murine skin [39]. During the following years, the resulting stress response has been further characterized in human and murine skin [37, 38]. Altogether, these studies provide compelling evidence that the oxidative stress response elicited by $O_3$ is not restricted to the stratum corneum, but cascades down into deeper layers of the skin, where it can activate transcription factors such as NFkB and aryl hydrocarbon receptor [37, 38]. Activation of cellular stress markers such as heat shock proteins has also been observed [37]. It was shown that exposure to $O_3$ can increase expression of matrix metalloproteinase-2 (MMP-2), enzyme responsible for cleaving type-IV collagen [40]. As MMP-2 cleaves type-IV collagen in the extracellular matrix and other substrates, including other MMPs, its activation triggers degradation of the extracellular matrix [40]. Such degradation, in turn, was shown to lead to clinical and histologic changes in the skin, which characterize coarse wrinkles [41].

### Interaction between Air Pollution and UV Radiation

The association between UV radiation and facial lentigines has been well-established in epidemiological studies [13–15], in human pigmented reconstructed skin [16] as well as in the mouse model [17].

Under physiologic conditions and in particular in urban environments, human skin is exposed to both solar UVA/UVB radiation and traffic-related air pollution. Solar UV radiation comprises UVC (100–280 nm), UVB (280–315 nm), and UVA (315–400 nm) radiation. From these, only UVA and UVB can penetrate the atmospheric ozone layer and thus have detrimental effects on the skin including photoaging and uneven skin pigmentation [4]. UVB radiation is the most energetic but only penetrates the superficial skin layers down to the epidermal basal layer. UVA is less energetic but is present in larger amounts and penetrates deeper into the skin reaching the dermis [4].

A recent epidemiological study showed that facial lentigines are the consequence of an interplay between UV and PM [24•]. The authors found a negative interaction between PM and UV on pigment spot formation: At higher PM levels, associations with UVB became weaker and, vice versa, at higher UVB levels, associations with PM became weaker.

Mechanistic studies showed that UVA as well as UVB are important for the degradation of PAHs and diesel exhaust particles (DEPs) leading to genotoxic and cytotoxic products [42–44]. These findings suggest a synergistic effect of UV and PM on human skin. However, the interplay between PM and UV in the troposphere is most likely more complex. Ohnuki et al. already indicated that the genotoxic products of PM and UV usually disappear in outdoor environments [43]. This assumption is in line with the epidemiological findings in [24•] because the authors did not observe any synergistic effects of PM and UV exposure on skin aging. Furthermore, the negative interaction that they observed between PM and UVB might be explained by the described degradation of PAHs by UV [42–44]. In addition, a shielding effect of photochemical smog might also be part of the explanation because traffic-related PM exposure is often highly correlated with $NO_2$, which is beside UV one of the controlling factors for the formation of photochemical smog [45].

## Conclusions and Future Research Directions

The association between traffic-related air pollution and skin aging has been well-established. While most studies have

studied associations with ambient PM exposure, there is also some evidence for associations with $NO_2$ as well as with indoor air pollutants. More recent epidemiological studies have further focused on the associations with ozone as well as interactions with UV radiation, a research area that is becoming more important with the increase of global warming.

## Limited Evidence on the Association Between $NO_2$ and Skin Aging

The association between PM and skin aging has been well-established over the last decade, and the profound evidence is based on epidemiological [18, 27–29] as well as mechanistic studies [20, 21, 31, 46]. In contrast, the association between $NO_2$ and skin aging has only been shown in two cohorts [22], and there is a lack of mechanistic evidence on this association. Since $NO_2$ is highly correlated with ultrafine particles as well as with black carbon, which are both mainly linked to traffic emissions [23], the associations found in [22] might rather support the well-established associations with chronic exposures to complex urban air pollution mixtures than showing an association with $NO_2$ itself.

## Limited Epidemiological Evidence on Ozone and Skin Aging

Over the last two decades, mechanistic studies have shown the harmful effects of ozone on murine skin [38–40, 47]. Recently, this strong mechanistic evidence has finally been confirmed in an epidemiological study: Fuks et al. showed in two independent population-based cohort studies that exposure to high levels of ground-level ozone ($O_3$) was associated with wrinkle formation in the face [19•]. This finding is particularly interesting and relevant because levels of ozone, which are directly linked to warmer temperatures caused by climate change, have been increasing in many western countries over the last years [48]. Despite this single confirmation of the mechanistic studies of ozone exposure on skin aging, more studies are needed to support the epidemiological evidence on this association.

## Limited Epidemiological Evidence on Interaction between UV Radiation and Air Pollution

Mechanistic studies of the last couple of years have shown a synergistic effect of UV and PM on human skin [42–44]. Recently, the interaction between UV and PM has been analyzed in a population-based setting by showing a negative interaction between PM and UV on pigment spot formation [24•]. These findings showed that the interplay between PM and UV in the troposphere is most likely more complex than can be modeled in laboratory-based experiments and that degradation of PAHs by UV [42–44] and a shielding effect of photochemical smog [45] might play an important role for the interaction between UV and PM. Since this study was conducted in a German cohort, in which UV levels were relatively low and varied only little within the study area, future interaction studies should focus on regions with higher UV radiation levels.

## Possible Mechanisms of Air Pollution-Induced Skin Aging

Current research suggests that each individual air pollutant most probably has a specific toxic action on the skin. There are two hypotheses on how air pollution might affect the skin, one is the outside-inside effect, e.g., penetration of pollutants directly into the skin. However, penetration of air pollution into the skin is not well-investigated and depends on the size and chemical composition of the pollutant. While it is known that ozone exposure can cause a variety of adverse reactions in the upper and deeper skin layers [49], evidence is limited on the mechanisms of the effects of other air pollutants. The other pathway that is hypothesized is the inside–outside mechanism, e.g., PM-induced systemic inflammation in the lung and subsequently the circulation [37]. However, it is unknown which of the pathways or a combination of the two explains the association between air pollution and skin aging.

## Future Directions: Interactions of Environmental and Genetic Risk Factors with Air Pollution and the Role of Epigenetics

In real life, the skin is not only affected by air pollution and UV but also by many other genetic and environmental factors, e.g., tobacco smoke and nutrition, which are summarized under the concept of skin aging exposome [4]. While there has already been substantial evidence about the associations of many of these environmental (summarized in [4]) and genetic [50–53] risk factors with skin aging, very little is known about their interactions with air pollution.

The only environmental factor for which we have at least some evidence about its interaction with air pollution is nutrition: It has been estimated that nutrition may account for up to 30% of wrinkle formation [54]. The accumulation of reactive oxygen species (ROS) has been reported to induce skin aging through the expression of MMPs, including MMP-1, MMP-2, and MMP-9 [55]. Consequently, antioxidants might have a protective effect on skin aging. Some evidence on a protective role of antioxidants on air pollution-induced skin aging comes from a study by Hyun et al. who showed that in human keratinocytes fermented fish oil inhibited the $PM_{2.5}$-induced generation of intracellular ROS and MMPs, including MMP-1, MMP-2, and MMP-9 [56]. In addition, fermented fish oil significantly abrogated the elevation of intracellular $Ca_{2+}$ levels in $PM_{2.5}$-treated cells and was also found to block the

$PM_{2.5}$-induced mitogen-activated protein kinase/activator protein 1 (MAPK/AP-1) pathway [56]. However, more studies are needed to fully understand the role of antioxidants on air pollution-induced skin aging.

Another area with growing importance for aging research is epigenetics, which is often seen as a proxy for the combined influences of genetics and environment. Telomere length and DNA methylation have been known as excellent markers for aging and aging-related diseases [57], and studies on skin tissue have shown that telomere length and DNA methylation markers in the epidermis are a good predictor of aging in general [58, 59] and skin aging in particular [58, 60]. As telomeres can be considered as the cellular memories of exposure to oxidative stress and inflammation, telomere maintenance may be a proxy for assessing the skin aging exposome, and epigenetics might provide new avenues for future preventive strategies of air pollution-induced skin aging [61].

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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