



Exposome and Skin: Part 1. Bibliometric Analysis and Review of the Impact of Exposome Approaches on Dermatology

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ABSTRACT

Introduction: Most skin disorders, such as atopic dermatitis, psoriasis, skin cancer or age-related skin issues, are the result of a complex interaction between genetic and environmental factors over time. As an external organ, the skin provides the opportunity to study the link between exposure to the environment and several specific biological responses using an

exposome approach. The aim of this review was to identify the state of the art of exposome approaches and elucidate the impact of the new era of exposomics on dermatology.

Methods: Two parallel and independent bibliometric analyses were conducted based on documents extracted from the Core Collection and the Science Citation Index Expanded (SCI-Expanded) databases from the Clarivate Analytics' Web of Science (WOS) platform by using the following search terms "exposome" and "skin exposome". In both searches, we used the topic field that includes title, abstract, author keywords and keywords plus terms and the following filters: "English language" and all documents published up to 30 September 2021. We further analysed and interpreted documents extracted in plain text format.

Results: Based on the defined searches, 910 documents were identified as being related to "exposome" and 45 as being related to "skin exposome". Environmental sciences and toxicology were the most impacted research areas, and aging, cancer and respiratory allergies were the most documented diseases while, surprisingly, dermatology was much less impacted. Krutmann et al. were the pioneers in implementing this new concept in dermatology with publication of "The skin aging exposome" in 2017 (J Dermatol Sci. 2017;85:152–61). After this tipping point, the number of publications in dermatology evaluating the impact of

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exposome factors in many skin disorders has steadily increased.

Conclusions: Exposome studies are rapidly attracting interest in dermatology. The results of these studies will undoubtedly improve our understanding of why and under which circumstances some individuals develop skin disorders and help design tailored prevention strategies for patients suffering from these disorders.

Keywords: Bibliometric analysis; Dermatology; Environmental factors; Epidemiology; Exposome; Exposure; Omics; Skin

Key Summary Points

Skin disorders are highly influenced by exposure to several environmental, lifestyle and internal factors that act on the genome, producing a specific biological response in the body.

The epidemiologist Christopher P. Wild coined the term “exposome” in 2005 to mean the lifelong totality of environmental exposure (including lifestyle factors) from conception.

Many exposome studies have been published in the fields of environmental sciences and toxicology, but dermatology has been much less impacted.

After the appearance of the pioneer publication in the *Journal of Dermatological Science* entitled “The skin aging exposome” in 2017, the number of publications relating to dermatology has increasingly grown.

Exposome studies might contribute to our understanding of the aetiology of skin disorders and help in the design of tailored preventive strategies for patients suffering from these disorders.

INTRODUCTION

Most skin disorders, such as atopic dermatitis (AD), psoriasis, skin cancer or age-related skin issues, are the result of a complex relationship between genetic and environmental factors which interact with each other over time [1–4]. To understand this complex interaction, it is crucial to know why and under which circumstances some individuals develop these skin disorders. However, the rapid progress that has been made in genetics in the last few decades with the Human Genome Project has tilted the genetic–environment balance in favour of the former [5–7]. The epidemiologist Christopher P. Wild realized the urgent need to develop methods for assessing an individual’s exposure and coined the term “exposome” in 2005 to mean the lifelong totality of environmental exposure (including lifestyle factors) from conception [8]. Clearly, the study of the exposome is a great challenge due to its high variability and dynamism and its full characterization would require repeated measures that capture exposure over a series of extended periods. Since many exposures will leave their fingerprint, the new “omics” technologies could help to tackle this great challenge of assessing exposure [9]. Despite the exposome concept first being introduced in the field of exposure assessment, it should also be extended to explain how our bodies respond to environmental pressures, including epigenetic modifications and complex biochemical reactions. Accordingly, the definition has been widened to: “The cumulative measure of environmental influences and associated biological responses throughout the lifespan, including exposures from the environment, diet, behaviour and endogenous processes” [10]. The skin is the outermost and largest organ, comprising a 2-m² interface that is constantly exposed to environmental factors, such as solar radiation, climate and pollution, whose effects have been studied and described in depth [11–13]. The effects of lifestyle factors such as, for example, nutrition or tobacco use have also been well described [14, 15]. Despite being an external organ, the skin is also exposed to endogenous stimuli, such as hormones [16],

microbiome [17] or even psychological stress [18]. The aim of our study was to identify the state of the art of exposome approaches and to elucidate what the impact of the new era of exposomics has been on dermatology. Here we present two bibliometric analyses of the exposome and skin exposome literature. We first present a quantitative analysis characterizing the body of literature, including annual scientific production and citations, the most impacted research areas, the salient authors and their intellectual roots and then we present a summary of all skin exposome publications.

METHODS

The bibliometric analyses were conducted as follows: (1) definition of the search criteria, including terms, language, period and database selection; (2) data extraction in plain text format; (3) data analysis, visualization and interpretation.

Search Strategy and Database

The search was conducted in the Core Collection and Science Citation Index Expanded (SCI-Expanded) databases from the Clarivate Analytics Web of Science (WOS) platform. We conducted two separate and parallel searches in September 2021, one related to the exposome and the other related to the skin exposome. Accordingly, we used the term “exposome” for the first search and the term “skin exposome” for the second one. We used a topic field which includes title, abstract, author keywords and keywords plus terms and the following filters: “English Language” and publication date up to 30 September 2021 for both searches.

Data Extraction

All documents related to the search term “exposome” were retrieved for further analysis, and those related to the search term “skin exposome” were manually selected to ensure search accuracy. We extracted the full record data and cited references in plain text format.

Data Analysis and Visualization

Based on the extracted data, two bibliometric analyses were performed using R software version 1.3.1056 [19] and the bibliometrix R package developed by Aria and Cucurullo [20]. For the construction of maps of co-occurrence analysis of author keywords, we used the VOS Viewer software (version 1.6.15; Leiden University Centre for Technology Studies, Leiden, the Netherlands) [21].

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Evolution of the Exposome Concept and Its Impact on Dermatology

Based on the defined searches, we found 910 documents related to “exposome” and 45 related to “skin exposome”. We retrieved all of the documents related to “exposome” and manually selected and retrieved 26 documents related to “skin exposome”. There has been a significant increase in scientific interest in the exposome concept since its definition in 2005, as evidenced by the number of publications (Fig. 1). In comparison, interest in this concept in dermatology has come later and involved fewer publications. As shown in the tree map of the top ten most frequent WOS research areas (Fig. 2), the top three research areas with the largest number of publications were “Environmental Sciences”, “Public Environmental Occupational Health” and “Toxicology”, with 253, 227 and 131 entries, respectively. Exposome-related concepts have also been exported to other disciplines, such as “Biochemistry Molecular Biology”, “Chemistry Analytical”, “Genetics Heredity”, “Immunology”, “Biochemical Research Methods”, “Respiratory System” and “Allergy”, among many others. Twenty-seven entries were classified in the “Dermatology” field, indicating that this discipline has been much less impacted by the exposome.

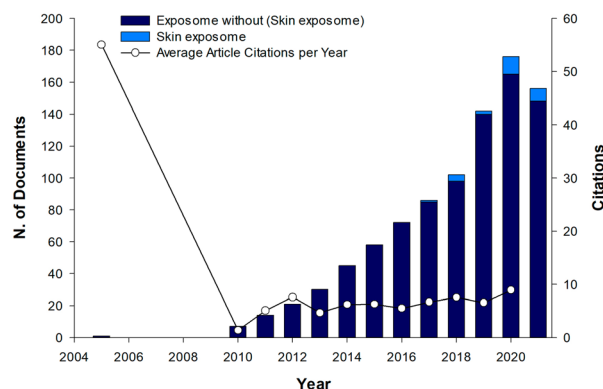


Fig. 1 Annual scientific production (column graph and left ordinate axis) and average number of article citations per year (line scatter graph and right ordinate axis) of the “exposome” and “skin exposome” documents obtained from the Clarivate Analytics Web of Science (WOS) platform.

The average number of article citations per year was calculated as the total sum of citations of all articles divided by the number of articles published in that year, then divided by the number of citable years

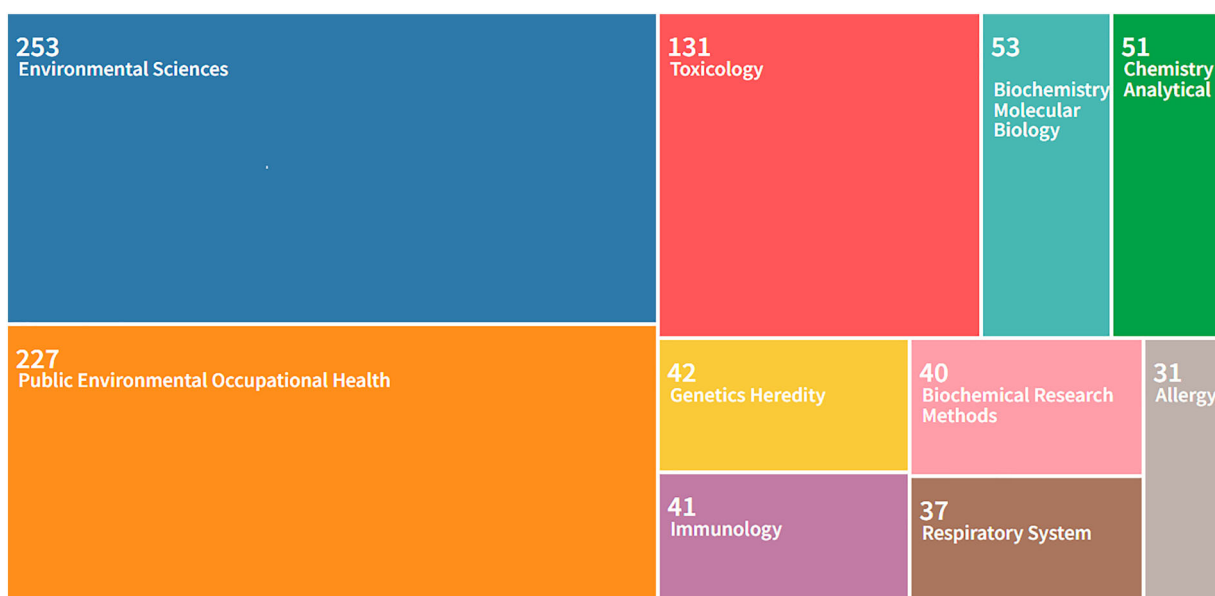


Fig. 2 Tree Map chart of the most impacted WOS categories

Co-Occurrence Analysis of Author Keywords in the 910 Documents Associated to “Exposome”

The density map of co-occurrence analysis of author keywords (Fig. 3), includes nine clusters of 94 relevant keywords with a total link strength of 526.5. In this map, we found that the main author keywords are “exposome”,

“environment”, “metabolomics”, “air pollution”, “biomarkers”, “epidemiology”, “pregnancy” and “asthma”, among many others. The most extensive clusters were related to aging, gut disorders, AD, biomonitoring and exposure assessment, respiratory allergies and cancer, among others.

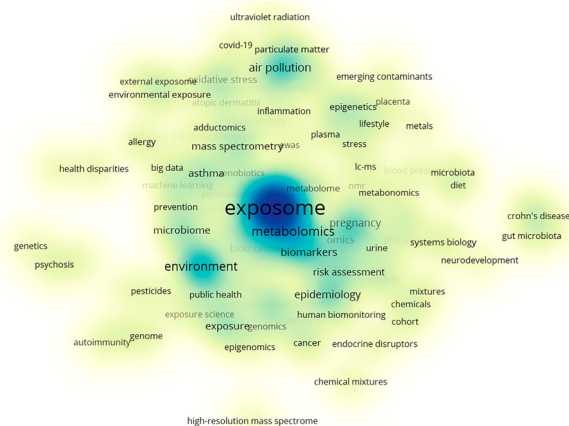


Fig. 3 Density visualization map of co-occurrence analysis of author keywords of the “exposome” documents. Counting method: fractional counting (the weight of a link is fractionalized). The relatedness of items was

determined based on the number of documents in which they occur together. Minimum number of occurrences of a keyword: 5

Review of the Exposome Implementation in Dermatology

The implementation of the exposome concept in dermatology started about 5 years ago and is growing rapidly (Table 1) [22–47]. The overall aim of most studies has been to evaluate the combined and cumulative effects of the exposome factors on skin health. In the following subsections we provide an update and general description of the skin exposome publications structured by pathology.

Skin Aging

Krutmann et al. were the pioneers in implementing this new concept in the field of dermatology with the publication entitled “The skin aging exposome” in 2017. They studied the role of exposome in skin aging and proposed the following categories of environmental factors: (1) sun radiation, ultraviolet radiation (UVR), visible light and infrared radiation; (2) air pollution; (3) tobacco smoke; (4) nutrition; (5) a number of less well-studied, miscellaneous factors; and (6) cosmetic products [47]. Based on their results, they concluded that UVR, smoking and pollution were the three main factors that induce skin aging [47]. Since this review, there have been several publications, including an in vitro study of the role of a mineralized

thermal water product to counteract the effects of the exposome on skin aging [44] and its possible role in improving facial skin quality when combined with hyaluronic acid in vivo [42]. A cross-sectional epidemiological study analysed the impact of various factors on the degree of skin aging among the Spanish population [34]. Khmaladze et al. reviewed the impact of environmental, lifestyle and internal factors on skin health and skin aging and constructed a digital model to identify and optimize skin treatment options based on external triggers [38]. Later studies have assessed how the impact of cigarette smoke alters the skin barrier [30], and what type of daily photoprotection is needed to mitigate extrinsic skin aging [26]. Clearly, skin aging has been the most impacted pathology by the exposome concept in the field of dermatology.

Atopic Dermatitis

Regarding AD, Ghosh et al. explored the subphenotypes/endotypes that result from the complex interplay between intrinsic and extrinsic factors through a multi-omics approach, integrating data from different layers, such as the microbiome, proteome, lipidome, transcriptome, epigenome, exposome and genome, unravelling new biological insights in the aetiology of this complex disease [43]. Cecchi

Table 1 Skin exposome publications

Study title	Year	Total number of citations	Journal	Disease(s) analysed	Exposome factors analysed
How to prevent skin damage from air pollution part 2: Current treatment options [22]	2021	0	<i>Dermatol Ther</i>	Acne, airborne allergic contact dermatitis, AD, dermatomyositis, lupus erythematosus, NMSC, rosacea and skin aging	Pollution
Diet-related phototoxic reactions in psoriatic patients undergoing phototherapy: results from a multicenter prospective study [23]	2021	0	<i>Nutrients</i>	Phytophotodermatitis, erythema	Vegan, vegetarian and omnivore diet, NB-UVB
Exposome extrinsic factors in the tropics: the need for skin protection beyond solar UV radiation [24]	2021	0	<i>Sci Total Environ</i>	–	Solar UVR, air pollution, air temperature, relative humidity and ground level ozone (O ₃)
Adult skin acute stress responses to short-term environmental and internal aggression from exposome factors [25]	2021	0	<i>J Eur Acad Dermatol Venereol</i>	–	Environmental (meteorological factors, solar radiation and pollution) and internal (acute nutrition / alcohol intake, hormonal variations, lack of sleep, psychosocial stress)
Daily photoprotection to prevent photoaging [26]	2021	3	<i>Photodermatol Photoimmunol Photomed</i>	Skin aging	Solar UVR, VL, IRA and pollution

Table 1 continued

Study title	Year	Total number of citations	Journal	Disease(s) analysed	Exposome factors analysed
Impact of ultraviolet radiation and exposome on rosacea: Key role of photoprotection in optimizing treatment [27]	2021	1	<i>J Cosmet Dermatol</i>	Rosacea	UVR, VL, pollution, tobacco, nutrition, stress, heat, cleansers, moisturizers, sunscreens
The role of photoprotection in optimizing the treatment of atopic dermatitis [28]	2021	0	<i>Dermatol Ther</i>	Atopic/contact dermatitis	UVR, vitamin D, sunscreens
SkinBug: an artificial intelligence approach to predict human skin microbiome-mediated metabolism of biotics and xenobiotics [29]	2021	0	<i>ISCIENCE</i>	–	–
Impact of cigarette smoke on physical–chemical and molecular properties of human skin in an ex vivo model [30]	2020	1	<i>Exp Dermatol</i>	Skin aging	Cigarette smoke
Clinical and biological impact of the exposome on the skin [31]	2020	11	<i>J Eur Acad Dermatol Venereol</i>	Skin aging, AD, rosacea, acne, psoriasis	Solar radiation, pollution, hormones, nutrition & psychological factors
Skin exposome science in practice: current evidence on hair biomonitoring and future perspectives [32]	2020	1	<i>J Eur Acad Dermatol Venereol</i>	Hair damage	Pollution and microbiome
Environmental factors in epithelial barrier dysfunction [33]	2020	29	<i>J Allergy Clin Immunol</i>	AD, other respiratory disorders	Allergens, detergents, tobacco, ozone, pollution, nanoparticles, microplastic

Table 1 continued

Study title	Year	Total number of citations	Journal	Disease(s) analysed	Exposome factors analysed
Study of the exposome ageing-related factors in the Spanish population [34]	2020	3	<i>Acta Derm Venereol</i>	Skin aging	Solar radiation, sunscreens, cosmetics, nutrition, water intake, alcohol, tobacco, stress level, sleep deprivation
The role of exposome in acne: results from an international patient survey [35]	2020	10	<i>J Eur Acad Dermatol Venereol</i>	Acne	Sun exposure, humid or hot, weather, mechanical factors, stress, pollution, nutrition, nibbling, tobacco
Gut microbiota and nutrient interactions with skin in psoriasis: a comprehensive review of animal and human studies [36]	2020	3	<i>World J Clin Cases</i>	Psoriasis	Nutrition, microbiome
Balance between health risks and benefits for outdoor workers exposed to solar radiation: an overview on the role of near infrared radiation alone and in combination with other spectral bands [37]	2020	3	<i>Int J Environ Res Public Health</i>	Skin cancer, skin aging, macular degeneration	Solar radiation (IRA, UVB, UVA, visible light)
The skin interactome: a holistic “genome–microbiome–exposome” approach to understand and modulate skin health and aging [38]	2020	2	<i>Clin Cosmet Investig Dermatol</i>	Skin aging	UVR, blue light, IRR, pollution, climate, sleep, exercise, nutrition, mental health, pre- and probiotics, cosmetics, microbiome

Table 1 continued

Study title	Year	Total number of citations	Journal	Disease(s) analysed	Exposome factors analysed
How to prevent skin damage from air pollution. Part 1: exposure assessment [39]	2020	3	<i>Dermatol Ther</i>	–	Pollution
Using wearable devices for assessing the impacts of hair exposome in Brazil [40]	2019	7	<i>Sci Rep</i>	Hair damage	UVR, temperature, humidity, ozone, pollution and chemicals
The exposome in atopic dermatitis [41]	2020	36	<i>Allergy</i>	AD	UVR, temperature, humidity, pollution, water hardness, allergens, microbiome, nutrition
A review of protection against exposome factors impacting facial skin barrier function with 89% mineralizing thermal water [42]	2019	7	<i>J Cosmet Dermatol</i>	Skin aging	Solar radiation, pollution, tobacco, nutrition, stress, sleep deprivation, cosmetics
Leveraging multi-layered “omics” data for atopic dermatitis: a road map to precision medicine [43]	2018	26	<i>Front Immunol</i>	AD	–
Vichy thermal spring water (VTSW), a cosmetic ingredient of potential interest in the frame of skin ageing exposome: an in vitro study [44]	2018	5	<i>Int J Cosmet Sci</i>	Skin aging	–
The influence of exposome on acne [45]	2018	36	<i>J Eur Acad Dermatol Venereol</i>	Acne	Nutrition, psychological & lifestyle, occupational, pollution, medication, climatic factors

Table 1 continued

Study title	Year	Total number of citations	Journal	Disease(s) analysed	Exposome factors analysed
External exposome and allergic respiratory and skin diseases [46]	2018	71	<i>J Allergy Clin Immunol</i>	Respiratory allergies and AD	Pollution, dust, aeroallergens, climate, microbiome
The skin aging exposome [47]	2017	223	<i>J Dermatol Sci</i>	Skin aging	Solar radiation, pollution, tobacco, nutrition, psychological stress, sleep deprivation, temperature, cosmetics

AD Atopic dermatitis, *IRA* infrared A, *IRR* infrared radiation, *NB-UVB* narrow-band ultraviolet B, *NMSC* non-melanoma skin cancer, *UVA* ultraviolet A, *UVR* ultraviolet radiation, *VL* visible light

et al. investigated the effects of both the external and internal exposome on respiratory allergies and AD [46]. These authors stratified the external exposome into nonspecific factors (climate, biodiversity, socioeconomic factors) and specific external factors (e.g. allergens, pollution and diet) [46]. Similar to this model, Stefanovic et al. reviewed the influential role of exposome factors in the aetiology and clinico-pathological diversity seen in AD patients, highlighting several multi-level exposome manipulation approaches from the population to individuals as preventative strategies and proposing future directions for exposome characterization and modification [41]. Sözener et al. discussed the harmful effects of environmental factors, including allergens, pollution and plastics, on epithelial barrier integrity and partly explained how they can trigger barrier disruption and tissue inflammation, leading to the appearance of atopic and also respiratory and gut diseases [33]. Piquero-Casals et al. reviewed the role of UVR and the exposome in

the aetiology of AD, as well as the role of adequate photoprotection [28].

Acne

Dréno et al. were the pioneers in implementing this concept on acne and classified the impact of exposome factors by means of a review of the following six main categories: nutrition, medication, occupational factors (including cosmetics, pollutants, climatic factors) and psychological and lifestyle factors [45]. Data from an international survey added new evidence and confirmed the assumptions made in the literature review mentioned above [35].

Psoriasis

Damiani et al. addressed the psoriasis exposome by means of a review focused on the skin–microbiome–gut–nutrient interaction and suggested that diet could be modulating the gut microbiome and that the latter, in turn, could be modulating the systemic inflammatory response in the body [36].

Rosacea

Morgado-Carrasco et al. described the aetiology of rosacea with an emphasis on the role of UVR and exposome and explained how several environmental factors, such as UV light, diverse microorganisms, air pollution, tobacco smoking, nutrition and psychological stress trigger or worsen this disorder [27].

Miscellaneous

Passeron et al. reviewed the impact of exposome factors, including solar exposure, air pollution, hormones, nutrition and psychological factors, on skin aging and other skin pathologies, such as AD, psoriasis, acne and rosacea [31]. Pacifico et al. evaluated the clinical outcomes of vegan, vegetarian and omnivore psoriatic patients undergoing ultraviolet B phototherapy and found that vegetarians consume foods containing photosensitizers capable of triggering phytophotodermatitis and that vegans have a higher risk of severe erythema [23]. Two meteorotropic studies assessed the real-life exposure conditions during routine daily activities on hair fibres and skin, carried out in Rio de Janeiro, by using multiple sensors to capture UVR, temperature, relative humidity, air pollution and ground level ozone levels [24, 40]. Damevska et al. reviewed qualitative and quantitative skin exposure assessment methodologies to air pollution [39], and subsequently published a second review focusing on how air pollution triggers or aggravates dermatoses [22]. Apenzeller et al. proposed hair biomonitoring as an alternative to biological fluids for assessing chronic exposure to environmental factors since hair analysis gives access to information covering a much wider temporal window than urine and blood [32]. These authors also discussed further approaches and perspectives to characterize and treat the skin exposome [32].

Social and Intellectual Interactions in the “Skin Exposome” Documents

Based on “skin exposome” documents and with the aim of identifying the relationship between the most salient authors, their publications and the most relevant references in their works, we

constructed a three-field plot showing the flow of information among them. The most prolific authors identified in our three-field plot were A Boulloc, J Krutmann, T Passeron, CC Zouboulis, ML Andersen and R Katta, as well as many others (Fig. 4). The cited references shown in this three-field plot include the first definition of the exposome concept [8] and a later reworked definition [10]. The remaining cited references include the first publication of the exposome in dermatology and several articles which focus particularly on the consequences and clinical impact of pollution on the skin, the effects of UVR and infrared radiation and the impact of other exposome factors on skin aging, acne, psoriasis and other skin-related disorders.

DISCUSSION

Since publication of the exposome concept in 2005, there has been a steady increase in the number of publications associated with this concept (Fig. 1), especially in the fields of environmental sciences and toxicology where aging, cancer and respiratory allergies are the most impacted diseases (Figs. 2, 3). Assuming that the skin provides an opportunity to link exposure to biological response, it is surprising that the first article in the field of dermatology related to the skin aging exposome was not published until 2017 [47]. After this signal event, increasingly more research groups in dermatology have assessed the impact of environmental factors on skin, especially on skin aging [26, 30, 31, 34, 37, 38, 42, 44], psoriasis [31, 36], acne [31, 35, 45], AD [31, 33, 41, 43, 46] and rosacea [27], through an exposome approach. Clearly, skin aging and AD have been greatly impacted by the exposome concept, while skin cancer has been less impacted by this new approach, leading us to review here the influential role of the exposome in non-melanoma skin cancers, specifically actinic keratosis, squamous cell carcinoma and Bowen’s disease. The exposome concept will bring new insights and consolidate a new era of research since most skin disorders are the result of a complex interaction between genetics and the environment [1–4]. In addition, the holistic part of the exposome concept

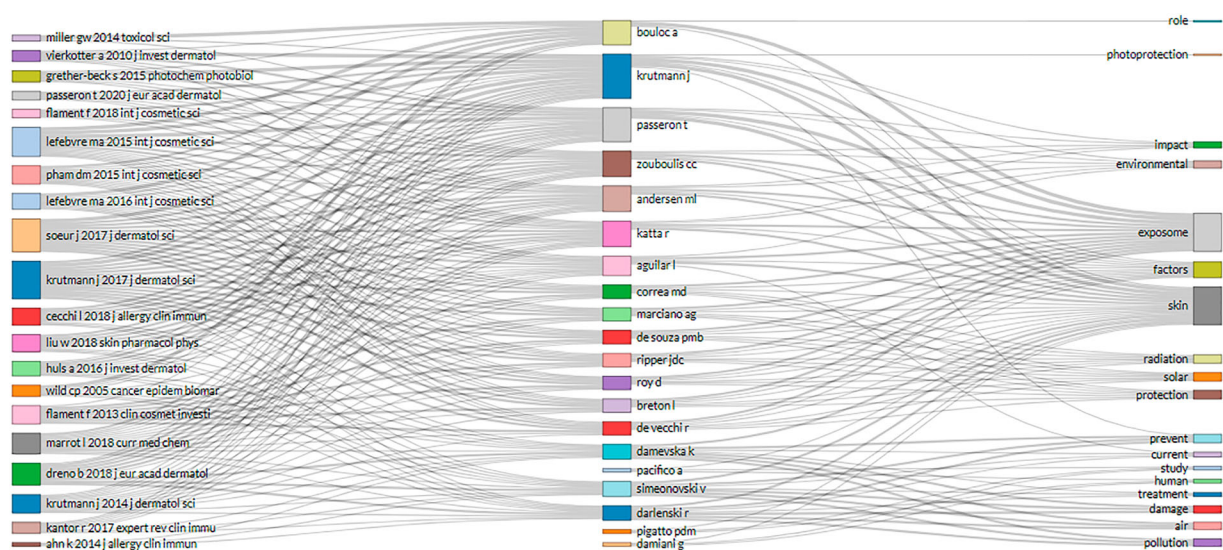


Fig. 4 Three-fields plot showing the relationship between references (left column), salient authors (middle column) and titles (right column) in the “skin exposome” documents

could help to unravel the complex interactions which occur between the different exposome factors and their associated biological consequences.

Historically, the impact of the exposome factors on skin has been studied separately, and the molecular crosstalk between the distinct factors and biological response is poorly understood, as suggested by Krutmann and colleagues in the skin aging example [47]. When the impact of a number of exposome factors combined is studied, the biological results and consequences cannot be explained by the cumulative effect of each one separately, suggesting there might be a synergistic effect and molecular crosstalk between them that can only be elucidated through an exposome approach. In addition to the environmental interactions, exposome approaches should be studied and interpreted against the genetic background of the population to create the most accurate disease prediction model as possible, thereby enabling the design of tailor-made prevention strategies. Most of the skin exposome studies published to date (Table 1) [22–47] are reviews that examine studies evaluating the effect of exposome factors individually; consequently, interaction effects are probably missed and not taken into consideration. There has been no environment-wide

association study (EWAS) published to date that evaluates the link between environmental variables and skin disorders in a high-throughput and unbiased manner, which would help to elucidate how exposure modulates pleiotropy, as in the example of diabetes [48]. In addition, most studies do not consider the environmental exposure effect of the prenatal period, and such assessment could provide insight into disease development since developmental periods in early life may be particularly vulnerable to the impact of environmental exposure [49], suggesting a developmental programming of the foetal phenotype through epigenetic modifications in order to prepare the individual for the predicted environment [50, 51]. In fact, the term “pregnancy” has been one of the most recurrent author keywords in the “exposome” publications (Fig. 3). Furthermore, there is an urgent need in dermatology to use integrative multi-omics approaches, as in the example of AD [43], which may bring new insight into the effect and interaction of all exposome factors and the associated human body response. Several publications on the exposome were related to both AD and allergies [33, 46]. This relationship could be explained by the atopic march, a model that explains the progression of allergies from AD to allergic asthma, allergic rhinitis and also food allergies, as all three (skin,

trachea and gut) are epithelial barriers exposed to environmental factors against the same genetic and immunological background [52]. In the case of psoriasis, a strong relationship with nutrients and the microbiome has been found since diet appears to play an important role in this disease and the gut microbiota could modulate systemic inflammatory disease [36].

Study Limitations and Strengths

This bibliometric analysis only offers a snapshot of what has been published until now, and no assertions can be made about the exposome and its impact on dermatology in the long run. In addition, the main limitation of this review is that only one database was used for data retrieval. Nevertheless, the WOS Core Collection platform is a curated collection of over 21,000 peer-reviewed, high-quality scholarly journals published worldwide. It is a selective, structured and balanced database with complete citation linkages and metadata with a wide range of information.

CONCLUSIONS

In conclusion, we believe that the exposome approach, which has had a low impact on dermatology in recent decades, is starting to quickly gain interest and will probably bring new insight into the understanding of the complex interactions between environmental factors and the associated biological responses. This great challenge could be overcome with “Big Data” analysis and integrative multi-omics; tailored prevention strategies could then be devised from these data and provide help for patients suffering from skin disorders.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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