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SYSTEMATIC REVIEW

Exposome Risk Factors for Vitiligo: A Systematic Evidence Review

Jaime Piquero-Casals[1] · Clémence Bertold[2] · Agustín Alomar[3] · Daniel Morgado-Carrasco[4] · Yolanda Gilaberte[5] · José Luis López-Estebaranz[6] · Antonio Massa[7] · Caio Silva de Castro[8] · Giovanni Leone[9] · Henry W. Lim[10] · Jean Krutmann[11] · Khaled Ezzedine[12,13] · Thierry Passeron[2,14]

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Abstract

Background Vitiligo is a multi-factorial autoimmune skin disorder often triggered by environmental exposures. Although the exposome has gained attention, no systematic review has fully assessed its role in vitiligo.

Objective We aimed to evaluate evidence linking exposomal factors to vitiligo onset and progression, focusing on quantifiable associations and study quality.

Methods A systematic search of PubMed and Embase (inception to 25 August, 2024) followed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines and was registered in PROSPERO (CRD42024529828). Eligible studies reported associations between environmental exposures and vitiligo onset, flares, or progression. Observational studies, case series, clinical trials, and pharmacovigilance reports were included. Findings were synthesized narratively.

Results Of 8377 records, 496 studies met inclusion criteria. Drug-associated vitiligo, particularly from immune checkpoint inhibitors, was the most robustly supported association (7–25% in patients with melanoma). Phenol-based chemicals were consistently linked to melanocyte toxicity. Coronavirus disease 2019 infection modestly increased risk (hazard ratio ≈ 1.11), while vaccination did not. Other factors such as stress ($n = 113$), trauma, sunburn, smoking, diet, and sleep were frequently cited but supported by lower-level evidence. Study heterogeneity, a lack of standardized outcomes, and the predominance of observational designs limited meta-analysis and causal inference.

Conclusions These findings highlight the environmental triggers of vitiligo onset and progression. Drugs, chemicals, and infections are key triggers; lifestyle factors require further study.

Key Points

Multiple environmental exposures, such as immunotherapy, phenolic compounds, and vaccines, have been linked to vitiligo onset or flares in genetically predisposed individuals.

This systematic review synthesizes evidence from nearly 500 studies, identifying high-consistency exposomal risk factors with clinical relevance for counseling and prevention.

1 Introduction

Vitiligo is a chronic autoimmune skin disorder characterized by melanocyte loss and progressive depigmentation, affecting approximately 0.5–2% of the global population. Vitiligo has a multi-factorial pathogenesis, involving genetic susceptibility and environmental triggers [1].

The exposome, first conceptualized as the totality of environmental exposures throughout an individual's life [2], plays a critical role in vitiligo by interacting with immune, oxidative, and neuroendocrine pathways. This framework extends beyond traditional risk factors, encompassing chemical agents, psychosocial stress, ultraviolet exposure, pollutants, infections, diet, and hormonal fluctuations [3]. In genetically predisposed individuals, these exposures may act as primary triggers or disease-modifying factors, accelerating melanocyte destruction through oxidative stress, immune activation, and loss of immune tolerance [4].

Despite increasing research on environmental influences in vitiligo, no comprehensive systematic review has quantified these associations or their clinical significance. This study aims to systematically evaluate the role of exposomal factors in vitiligo onset and progression to identify potential modifiable risk factors and guide

Khaled Ezzedine and Thierry Passeron have contributed equally to this work and should be considered co-last authors.

Extended author information available on the last page of the article

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preventive and therapeutic strategies. Unlike previous narrative overviews, this review integrates environmental, pharmacologic, and psychosocial factors within a unified exposome framework, highlighting their cumulative impact and evidence-based prioritization.

2 Methods

2.1 Protocol and Search Strategy

This systematic review followed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines [5] and was registered in PROSPERO (CRD42024529828). A comprehensive search of PubMed and Embase was conducted with the help of a scientific librarian affiliated to the Paris Public Hospitals' Documentation Center (CDOC, AP-HP), to build the search strategy, from inception through 25 August, 2024, using MeSH terms and free-text keywords related to vitiligo and environmental exposures. The full search strategy is detailed in the Electronic Supplementary Material (ESM). The list of keywords was developed based on prior reviews on the skin exposome and on the vitiligo pathogenesis. It was refined through a pilot PubMed search to ensure inclusion of less-reported environmental and lifestyle factors.

2.2 Eligibility Criteria

We included human studies reporting associations between exposomal/environmental factors and vitiligo onset, progression, or relapse. Eligible designs included observational studies (cohort, case-control, cross-sectional), clinical trials, and case series. Exclusion criteria were non-human studies, the absence of vitiligo-related outcomes or associations, or a lack of extractable data. However, studies without defined case/control numbers were retained if they offered relevant mechanistic or descriptive insights.

2.3 Quality Assessment

Study quality and risk of bias were assessed according to study design. Observational studies (cohort, case-control, and cross-sectional) were evaluated using the Newcastle–Ottawa Scale. Case series and descriptive studies were assessed using the Joanna Briggs Institute critical appraisal checklists, while randomized controlled trials were evaluated using the Cochrane Risk of Bias Tool.

Quality assessment focused on selection methods, exposure and outcome ascertainment, comparability of study groups, and completeness of reporting. Studies were not excluded based on quality alone; instead, methodological rigor was considered during data synthesis and evidence grading. Detailed quality assessments are provided in the Tables S1–S3 of the ESM.

2.4 Data Extraction and Synthesis

One author (JPC) extracted study characteristics (author, year, country, design, sample size, exposure, main findings) using a standardized form; discrepancies were resolved by discussion. Because of study heterogeneity, no meta-analysis was performed. Results were synthesized descriptively, emphasizing consistency, directionality, and quality of evidence for each exposomal factor. To ensure reproducibility and methodological rigor, study selection and data extraction were performed using standardized PRISMA 2020 procedures. Each study was evaluated with validated quality tools (Newcastle–Ottawa Scale, JBI, or Cochrane Risk of Bias). Findings were synthesized following a structured framework based on evidence consistency, biological plausibility, and study quality rather than frequency alone. A descriptive analysis was performed to quantify the frequency of exposomal factors associated with vitiligo. For studies reporting hazard ratio (HR) or risk ratio (RR) values, original estimates were cited; a meta-analysis was not feasible because of heterogeneity.

3 Results

The literature search identified 8377 records, of which 2785 duplicates were removed. After screening titles and abstracts, 676 full-text articles were assessed for eligibility, and 496 studies were included in the final review (Fig. 1). The full reference list of all studies included in the systematic review is provided in the ESM.

Among the 496 studies included, we conducted a descriptive analysis to quantify the frequency and nature of reported associations between exposomal factors and vitiligo. The most consistently supported associations involved drug exposure, notably immune checkpoint inhibitors (ICIs), phenol-based chemical agents, and vaccination, based on large cohort studies and mechanistic data replicated across multiple cohorts.

The most frequently reported factor was psychological stress (n = 113), followed by drug exposure (n = 91), chemical agents (n = 47), infections (n = 41), graft-versus-host disease (n = 28), diet (n = 26), vaccination (n = 26), and trauma (n = 23). Other exposures included sunlight (n = 14), pollution and smoking (n = 13), transplantation (n = 12), radiation (n = 11), environmental factors (n = 11), vitamin D (n = 9), oxidative stress (n = 9), energy-based devices (n = 7), sleep disturbance and pregnancy (n = 5 each), heat (n = 3), and alcohol (n = 2). Many of these, especially stress, trauma, and diet, were supported primarily

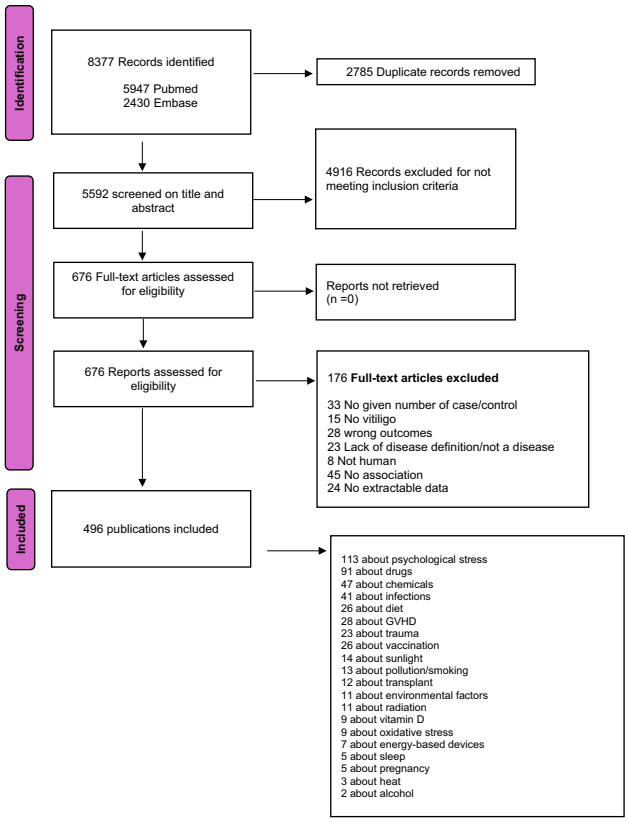

Fig. 1 PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram. *GVHD* graft-versus-host disease

by observational evidence and lacked consistency across cohorts.

Figure 2 illustrates the distribution of studies by factor. Table 1 summarizes both descriptive findings and available quantitative data across exposomal factors. Table 2 specifically presents the most robust, population-based adjusted risk estimates (hazard ratio/adjusted hazard ratio [HR/aHR]) derived from large cohort studies. Detailed results are presented in the following subsections. When available, HR/odds ratio (OR) data are prioritized as the most robust evidence.

3.1 Sunlight

No HR, OR, or RR estimates are available for sunlight exposure in vitiligo. Sun exposure in individuals with vitiligo presents a dual perspective. On the one hand, ultraviolet radiation used therapeutically (heliotherapy or phototherapy) can dampen immune responses and stimulate melanocyte stem cell differentiation, promoting repigmentation. On the other hand, patients often report the onset or worsening of lesions following intense sun exposure, particularly in chronically exposed areas such as the face and hands.

Although clinical data on sunlight as a trigger are limited, experimental studies have shown that ultraviolet A exposure induces oxidative stress in melanocytes and keratinocytes [6], supporting the biological plausibility of melanocyte damage from sun exposure. These non-human studies were included for mechanistic context only. In contrast, several clinical studies have specifically implicated severe sunburn, as opposed to chronic sun exposure, as a triggering factor for vitiligo flares in genetically predisposed individuals [7–9]. In these cases, sunburn acts as an acute environmental aggressor, inducing DNA damage, inflammation, and oxidative stress. A recent international survey also found that individuals with vitiligo frequently perceive an increased skin cancer risk and report high use of photoprotective measures [10].

3.2 Pollution and Smoking

Air pollution and smoking are distinct exposures that may contribute to vitiligo pathogenesis via overlapping mechanisms. Although chemically different, both are associated with oxidative stress, immune dysregulation, and melanocyte damage.

Exposure to ambient pollutants, such as particulate matter (PM2.5, PM10), ozone (O_3), and nitrogen dioxide, has been linked to skin barrier disruption, elevated reactive oxygen species, and inflammatory signaling [11]. While causality is unconfirmed, a Mendelian randomization study suggested a link between chronic exposure to coarse particulate matter and increased vitiligo risk [11], supported by a large Taiwanese cohort [12]. Mechanistically, pollutants such as polycyclic aromatic hydrocarbons activate the aryl hydrocarbon receptor (AhR), which regulates pigmentation, oxidative stress, and immune responses, suggesting melanocyte vulnerability in genetically predisposed individuals. Additionally, Enomoto et al. identified smoking as an independent risk factor for hand vitiligo (OR $\approx$ 3.1), further supporting a potential exposure–response relationship [13]. Smoking has shown inconsistent associations with vitiligo. A meta-analysis of case-control studies reported a higher smoking prevalence in patients with vitiligo (RR = 1.24, 95% confidence interval [CI] 1.06–1.46, $I^2 = 0\%$) [14], while a Korean cohort found a lower incidence among current smokers (HR = 0.69, 95% CI 0.65–0.72) [15]. Nicotine's potential immunosuppressive effects contrast with the pro-oxidant nature of tobacco smoke. Compounds such as carbon black and AhR ligands may alter melanocyte survival through both immune and pigmentary pathways.

3.3 Trauma, Chemical Exposure, and Heat

The Koebner isomorphic phenomenon is frequently observed in vitiligo, with lesions often appearing in areas of repeated trauma or friction, possibly due to melanocyte

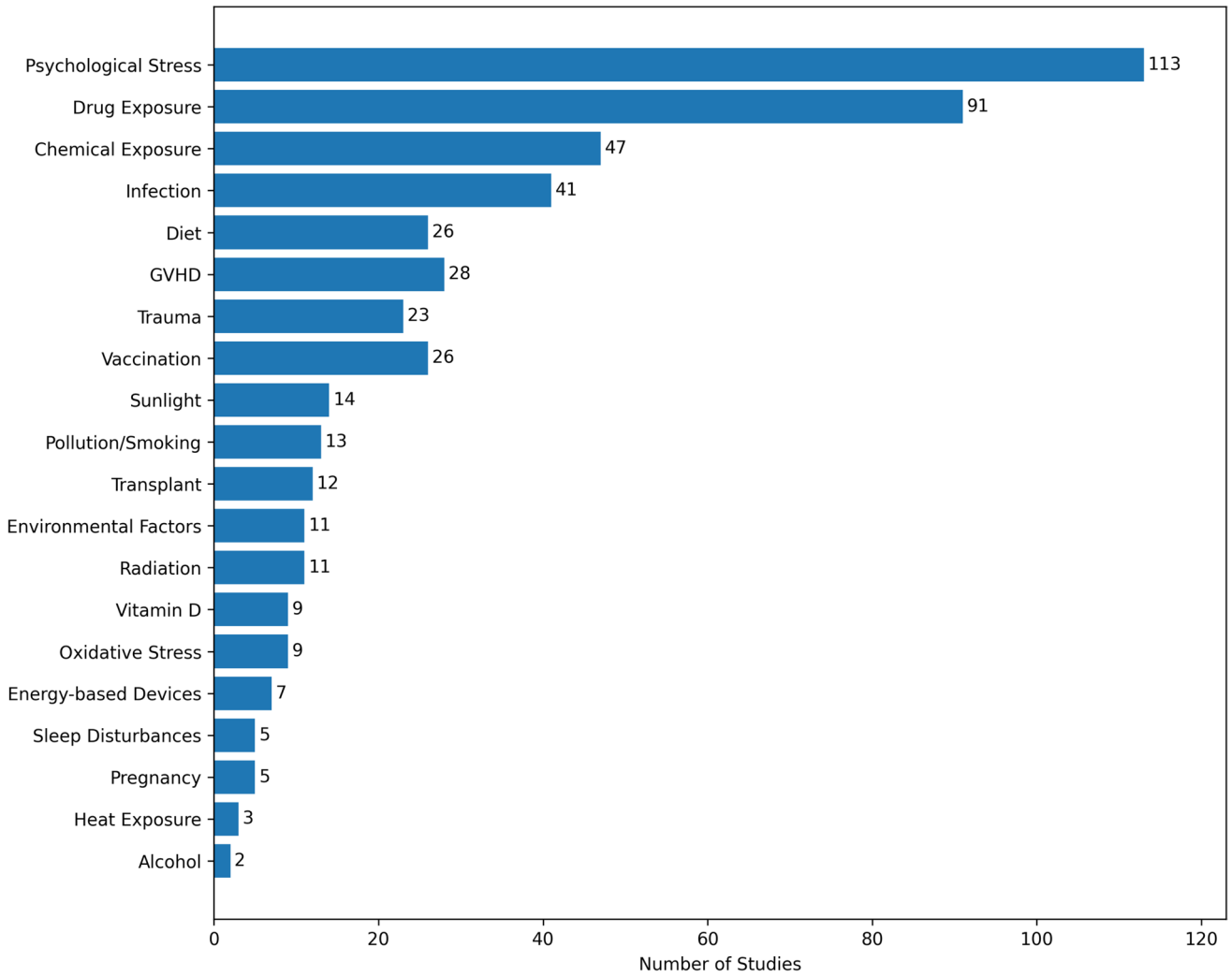

Fig. 2 Number of studies on exposomal factors in vitiligo. *GVHD* graft-versus-host disease

detachment from mechanical stress [16]. Low humidity and temperature may further increase this vulnerability [17].

Exposure to caustic chemicals, especially phenolic derivatives used in photographic developers, cosmetics, and industrial products, has been implicated in genetically predisposed individuals [18, 19]. Isolated reports also link tattooing and vaccination to lesion onset [18, 20]. The ViCEKb (Vitiligo-linked Chemical Exposome Knowledgebase) database lists 113 consumer-accessible chemicals with potential depigmenting effects, highlighting their structural and biological diversity [21]. Recent predictive toxicology approaches using machine-learning models have expanded the ViCEKb to encompass broader chemical families and predictive classification of vitiligo-linked compounds [22].

Chemical or thermal burns may contribute to melanocyte loss [23]. A large cohort study of 68,176 women found a borderline increased vitiligo risk among permanent hair dye users (aHR = 1.28), particularly with early or long-term use [24]. Patients with psoriasis or contact dermatitis may also be more susceptible to post-inflammatory vitiligo [25].

Radiation therapy [26], heat exposure [27], and friction from face masks [28] have been reported as triggers. Caution is advised with laser or intense pulsed light treatments, which may occasionally induce or worsen lesions [29].

3.4 Transplant Recipients

In a recent population-based cohort study involving 23,829 transplant recipients and 119,145 age- and sex-matched controls, transplant recipients exhibited a higher risk of vitiligo than the control group [30]. The greatest risk was observed in patients who had undergone hematopoietic stem cell transplantation, and those who received allogeneic grafts or experienced comorbid graft-versus-host disease had an

Table 1 Summary of exposomal factors and their impact

Factor	Number of studies	Key data (RR/HR)	Type of evidence	Interpretation
Psychological stress	113	Not quantified	Cross-sectional, case series	Frequently reported, low-quality evidence
Chemical exposure (phenols)	47	Mechanistic support; ViCEKb: 113 chemicals	Case reports + experimental	Strong biological plausibility
Immunotherapy	~ 40	7–25% incidence in melanoma	Large cohorts + mechanistic studies	Strong and consistent association
Vaccination	26	Temporal reports; cohort data neutral	Case series, pharmacovigilance one cohort showing no increased risk	Mixed findings; likely safe, but more data needed for rare outcomes
Alcohol	2	RR = 1.47 (95% CI 1.11–1.97)	Meta-analysis (case-control)	Moderate evidence
Smoking	~ 10	RR = 1.24/HR = 0.69	Case-control vs cohort	Inconsistent results
Sunburn	14	Not quantified	Case reports + mechanistic	Possible trigger
Physical trauma/Koebner phenomenon	23	Not quantified	Case reports + observational/ clinical studies	Clinically established trigger; observational evidence with high clinical relevance
Diet	26	Not quantified; CD 3.2% in vitiligo	Case reports + GWAS overlap	Weak evidence, no RCTs
Sleep disturbance	5	~ 50% prevalence ($n = 409$)	Case-control studies	Emerging evidence
Infection (e.g., CMV, HSV, SARS-CoV-2)	41	HR = 1.25 post-COVID	Case reports + virology studies Large cohort	Possible immunologic trigger; supported by population data after SARS-CoV-2
Oxidative stress	9	Not quantified	Mechanistic models	Pathophysiologically plausible
Hormonal changes (including pregnancy)	~ 6	Not quantified	Patient reported; weak data	Reported anecdotally
Transplant/GVHD	40 (28 GVHD, 12 transplant)	HR = ↑ in GVHD/↓ in solid organ	Cohort studies	High-quality data, but contrasting results
Energy-based devices (laser/ IPL)	~ 7	Not quantified	Case reports + expert opinion	Possible mechanical trigger
Radiation therapy	11	Not quantified	Case reports, review	Possible physical trigger
Physical activity	2	Not quantified	Narrative, indirect evidence	Emerging, mostly theoretical
Social media	2	Not quantified	Qualitative/observational	Relevant psychosocial factor, no clinical data

This table provides an extended summary of all exposomal factors reviewed in the article, including both quantitatively supported associations and those discussed descriptively. For some factors, no pooled relative risk (RR), hazard ratio (HR), or formal quantification was available, and these are marked accordingly. The table distinguishes between high-consistency associations and emerging or anecdotal findings

CD celiac disease, *CI* confidence interval, *CMV* cytomegalovirus, *GVHD* graft-versus-host disease, *GWAS* genome-wide association study, *HR* hazard ratio, *HSV* herpes simplex virus, *IPL* intense pulsed light, *RCTs* randomized controlled trials, *RR* relative risk, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *ViCEKb* Vitiligo-linked Chemical Exposome Knowledgebase

increased risk of vitiligo compared with individuals in the control group [30, 31]. Some cases may also reflect donor-derived autoimmunity, as vitiligo can be transferred from donors with pre-existing disease [32].

Conversely, another study focused exclusively on patients with solid organ transplants (14,712 patients and 44,136 controls) and revealed a significantly lower risk of developing vitiligo compared with controls [33]. It should be noted that these patients did undergo treatment with various immunosuppressants such as tacrolimus (60.36%), mycophenolate mofetil (53.81%), and cyclosporine (42.44%). These contrasting outcomes highlight the complexity of immune reconstitution and donor-related factors in post-transplant vitiligo.

3.5 Diet

A healthy diet, low in processed foods, refined sugars, and saturated fats, offers well-documented benefits. Anti-inflammatory and antioxidant-rich diets have shown efficacy in autoimmune diseases such as colitis and rheumatoid arthritis [34]. Several studies have suggested that diet and gut

Table 2 Quantified associations between exposomal factors and vitiligo

Exposomal factor	Measure of association	References
Severe sunburn (childhood)	HR = 2.17 (1.15–4.10)	Dunlap et al. (2017) [7]
Strong tanning response	HR = 2.59 (1.21–5.54)	Dunlap et al. (2017) [7]
Large melanocytic nevus	HR = 1.37 (1.02–1.83)	Dunlap et al. (2017) [7]
Smoking (current)	HR = 0.69 (0.65–0.72)	Lee et al. (2020) [15]
Hair dye use	HR = 1.28 (1.00–1.65)	Wu et al. (2015) [24]
Hepatitis C infection	aHR ≈ 6.45	Ma et al. (2022) [91]
Post-COVID-19 infection	aHR = 1.11 (1.04–1.19)	Heo et al. (2024) [96]
COVID-19 vaccination	aHR = 1.00 (NS)	Ju et al. (2023) [103]
PTSD	aHR = 16.06 (4.48–57.54)	Dai et al. (2021) [86]
Major depression	aHR = 7.24 (5.65–9.28)	Dai et al. (2020) [87]
Solid organ transplant	aHR = 1.73 (1.35–2.22)	Bang et al. (2023) [30]
Hematopoietic transplant	aHR = 12.69 (5.11–31.5)	Bang et al. (2023) [30]
Low vitamin D levels	Mean difference = −7.45 ng/mL	Upala et al. (2016) [104]

aHR adjusted hazard ratio, *COVID-19* coronavirus disease 2019, *HR* hazard ratio, *NS* not significant, *PTSD* post-traumatic stress disorder

microbiota composition may modulate oxidative balance in vitiligo [35, 36]. However, recommendations must be cautious when based on isolated case reports or lacking robust validation. In this context, a recent Japanese study identified high body mass index as an independent correlate of vitiligo and reported negative correlations between Vitiligo Area Scoring Index scores, age, and intakes of potatoes and non-green/yellow vegetables, although these associations require confirmation in other populations [37].

3.5.1 Gluten-Free Diet

Partial repigmentation has been reported in individual cases after initiating a gluten-free diet [38, 39]. In a cohort of 174 patients with vitiligo, celiac disease (CD) prevalence was 2.8% [40], and among 61 patients tested for CD markers, 23.8% were positive, yielding an overall rate of 3.2%. Conversely, vitiligo prevalence among patients with CD ranges from 1.8 to 9.1% [41–43]. Genome-wide studies show shared genetic variants between vitiligo and CD [44–46], suggesting the association may be genetic rather than dietary. No prospective randomized trials have demonstrated clear benefits of a gluten-free diet or other specific diets for vitiligo. Thus, due to limited and inconsistent data, no specific dietary regimen should currently be prescribed for patients with vitiligo.

3.5.2 Alcohol

A meta-analysis of two case-control studies (255 patients and 255 controls) found a 47% increased likelihood of heavy alcohol use among those with vitiligo (RR = 1.47, 95% CI 1.11–1.97; $I^2 = 0\%$) [47, 48]. One study showed a significant difference in alcohol dependence (32.3% vs 19.4%, $p = 0.013$) [47], while the other reported a non-significant trend (34% vs 27%, $p = 0.28$) [48]. The consistency and lack of heterogeneity support this association. More recently, Kamal et al. also reported increased odds of alcohol use disorder among patients with pigmentary disorders, including vitiligo [49]. Alcohol may also indirectly worsen vitiligo by contributing to stress, anxiety, and depression, factors frequently linked to disease onset and exacerbation.

3.6 Drugs

Various medications have been reported to be associated with, or to exacerbate, vitiligo, although the underlying mechanisms remain poorly understood. Documented drug-associated vitiligo cases include carbamazepine [50], chloroquine [51], tolcapone and levodopa [52], diphenylcyclopropenone [53], clofazimine [54], and beta-blockers [55]. The proposed mechanisms involve either sympathetic nerve damage or direct cytotoxicity leading to melanocyte apoptosis [56].

Biologic therapies have also been implicated in vitiligo onset. Interferon-alpha [57–59], tumor necrosis factor (TNF)-alpha inhibitors such as infliximab and adalimumab [60, 61], and immune-modulating drugs such as imiquimod and dupilumab [62, 63] have all been associated with vitiligo induction or progression. Patients with ankylosing spondylitis, Crohn's disease, or ulcerative colitis receiving anti-TNF therapy have a higher risk of vitiligo, likely owing to a cytokine shift favoring type I interferon signaling, which recruits autoreactive T cells targeting melanocytes [64–66].

Immune checkpoint inhibitors targeting programmed cell death protein 1 and cytotoxic T-lymphocyte antigen 4 have been widely associated with immune-related adverse events,

including vitiligo [67]. Vitiligo has been observed in 7–25% of patients with melanoma receiving ICIs, often correlating with improved prognosis [68]. This prognostic association has been independently confirmed in multiple melanoma cohorts, where the onset of vitiligo correlated with longer overall survival [69]. This phenomenon is attributed to cross-reactive T-cell responses against shared melanocyte and melanoma antigens [70]. Newer LAG-3 inhibitors, used alone or with ICIs, have also been linked to vitiligo-like depigmentation, likely via similar T cell-driven mechanisms [71].

CCR4 inhibitors (mogamulizumab), approved for cutaneous T-cell lymphoma, function via cytotoxic T-cell recruitment and depletion of regulatory T cells. This depletion may exacerbate autoimmunity, explaining vitiligo onset in treated patients [72].

Targeted cancer therapies, including tyrosine kinase inhibitors, frequently associate vitiligo-like hypopigmentation, particularly when targeting c-KIT, a key receptor in melanocyte survival and function. c-KIT inhibitors impair tyrosinase production, essential for melanin synthesis, thereby leading to melanocyte loss [73]. Similarly, cyclin-dependent kinase 4/6 inhibitors, widely used for metastatic breast carcinoma, have been reported to cause vitiligo, likely owing to off-target effects on melanocyte cell cycle regulation [74, 75].

3.7 Stress, Lack of Sleep, and Depression

3.7.1 Psychological Stress

Clinical and epidemiological evidence supports psychological stress as a major precipitating factor for vitiligo onset and flares. A prospective observational study linked early-onset vitiligo to prior psychological stress [76], an association replicated in over 140 studies involving more than 30,000 individuals [77, 78]. These findings underscore the role of neuroendocrine-immune interactions in vitiligo pathogenesis.

Stress activates the hypothalamic-pituitary-adrenal axis, raising catecholamine levels [79], and triggers the unfolded protein response in melanocytes, leading to endoplasmic reticulum stress and innate immune activation. Misfolded proteins act as danger-associated molecular patterns, stimulating CXCR3B-mediated inflammation [4]. Neuropeptides such as substance P and calcitonin gene-related peptide further disrupt immune regulation by interacting with dendritic cells, natural killer cells, and type 1 innate lymphoid cells, promoting melanocyte-targeted autoimmunity.

3.7.2 Chronic Lack of Sleep

Although direct studies are limited, sleep disturbances are frequent in vitiligo and may influence disease activity. In a case-control study of 409 patients, nearly half reported insomnia, often linked to disease activity or stress [80]. Another study noted increased parasomnias among patients with vitiligo, even before onset [81]. Chronic sleep loss promotes inflammation and oxidative stress through elevated interleukin-6 and TNF-α and circadian disruption [82, 83].

3.7.3 Depression

A strong bidirectional relationship exists between vitiligo and depression. Patients have higher rates of depression and anxiety, significantly impacting disease burden [84]. A meta-analysis reported a pooled prevalence of depressive symptoms of approximately one third among patients with vitiligo, one of the highest rates observed across dermatologic conditions [85]. Population-based cohort studies have also reported an increased risk of vitiligo among patients with major depressive disorder and post-traumatic stress disorder [86, 87].

Chronic depression may contribute to autoimmunity via elevated interleukin-1β, interleukin-6, and TNF-α levels [88, 89]. According to our evidence grading, these exposures fall within emerging or anecdotal categories because of limited and heterogeneous data.

3.8 Physical Activity and Sedentary Habits

No clinical studies have directly linked sedentary behavior to vitiligo onset or severity [90]. However, vitiligo is associated with metabolic syndrome, itself tied to inactivity and systemic inflammation [90]. Exercise may improve quality of life and body image in patients [84], and sustained physical activity may promote anti-inflammatory responses, antioxidant defenses, and mitochondrial health, potentially mitigating oxidative stress relevant to vitiligo pathogenesis [90].

3.9 Infection and Vaccination

Infectious triggers have long been proposed as potential contributors to vitiligo onset, particularly in genetically predisposed individuals. Case reports and small series have described vitiligo development following infections such as hepatitis C, HIV, herpes zoster, cytomegalovirus, and more recently, severe acute respiratory syndrome coronavirus 2 [91–95]. A large cohort study of over 15

million individuals supports an increased risk of vitiligo following severe acute respiratory syndrome coronavirus 2 infection [96]. Notably, cytomegalovirus DNA has been identified in skin biopsies of patients with vitiligo, raising the possibility of viral latency or local immune activation [97]. Histological findings such as varicella-zoster viral antigen and mature virions in segmental vitiligo lesions also suggest a possible viral contribution to melanocyte destruction [98]. Proposed mechanisms include activation of the innate immune system via pattern recognition receptors, or molecular mimicry, where melanocyte antigens resemble viral epitopes.

Recent population-based studies have quantified the potential association between COVID-19 vaccination and vitiligo. Shani et al. [99] reported increased rates of immune-mediated conditions after BNT162b2 vaccination (HR 2.82), and Kim et al. [100] found a similar autoimmune signal (HR 2.71). A Korean nationwide cohort showed a higher incidence of vitiligo after vaccination (aHR 2.22; 95% CI 1.54–3.19), whereas severe acute respiratory syndrome coronavirus 2 infection itself did not increase risk (aHR 0.95) [101]. These findings suggest a possible vaccine-related increase in vitiligo risk in specific populations, although further validation is needed. Numerous reports have described new-onset or exacerbated vitiligo following COVID-19 vaccination, often within days to weeks of immunization. A recent cross-sectional study and systematic review identified and analyzed these cases, supporting a plausible temporal and immunological link [102]. In contrast, a Korean cohort in almost 8 million individuals did not find any association between COVID-19 vaccination and vitiligo [103]. These findings warrant further investigation, particularly in individuals with underlying autoimmune tendencies.

3.10 Pregnancy/Hormonal Factors

Hormonal fluctuations may influence vitiligo progression, with puberty, pregnancy, childbirth, and menopause frequently reported by patients as periods of disease onset or exacerbation. Despite these clinical observations, data in the literature remain scarce.

While the exact mechanisms remain unclear, proposed explanations include systemic immune activation, heightened inflammatory responses, and hormonal fluctuations that may influence melanocyte function and survival.

Beyond pregnancy, vitamin D plays a well-recognized role in immune regulation, and low 25-hydroxyvitamin D levels (<15 ng/mL) have been reported in patients with vitiligo [104]. Although narrowband-ultraviolet B phototherapy increases circulating vitamin D levels, no randomized controlled trials have confirmed the benefit of vitamin D supplementation in vitiligo treatment [105].

3.11 Social Media

Acceptance of vitiligo-related appearance changes is often difficult, affecting employment, identity, and psycho-sexual well-being [106]. Social media presents both risks and benefits for individuals with vitiligo. Although robust data are lacking, platforms influence self-image and emotional health; engagement metrics may impact self-esteem, especially among youth [107]. While online scrutiny can heighten stress, social media also fosters community, education, and advocacy.

Figures like Winnie Harlow have helped normalize vitiligo. Despite limited formal research, clinicians should recognize the dual impact of social media in either reinforcing distress or promoting empowerment.

4 Discussion

This review systematically assessed exposomal factors associated with vitiligo onset or progression. While numerous environmental triggers have been proposed, only a few demonstrate consistent associations across high-quality studies. Across all exposomal domains, oxidative stress and immune dysregulation emerged as converging mechanisms linking diverse environmental triggers. Figure 3 provides an integrative overview of the main exposomal factors associated with vitiligo, highlighting the relative strength of evidence supporting each association.

Drug-associated vitiligo, especially from ICIs and biologic therapies, are strongly supported by cohort data and mechanistic evidence involving autoreactive T cells. Similarly, phenol-based chemical exposures from cosmetic or industrial sources show robust links to melanocyte cytotoxicity in both clinical and experimental contexts. Post-infectious vitiligo, particularly after COVID-19, is also supported by population-level data, suggesting plausible temporal and immunologic connections in genetically predisposed individuals.

Other factors such as psychological stress, dietary patterns, and sleep disturbances are frequently reported but supported by heterogeneous, mostly observational data. These exposures may act more as modulators than primary triggers. Smoking is a discordant example, with cohort studies suggesting a protective effect, possibly via AhR pathway modulation, contrasting with higher prevalence in case-control data.

A key limitation is the lack of large prospective studies directly examining environmental exposures and vitiligo. Many included studies were case reports or lacked

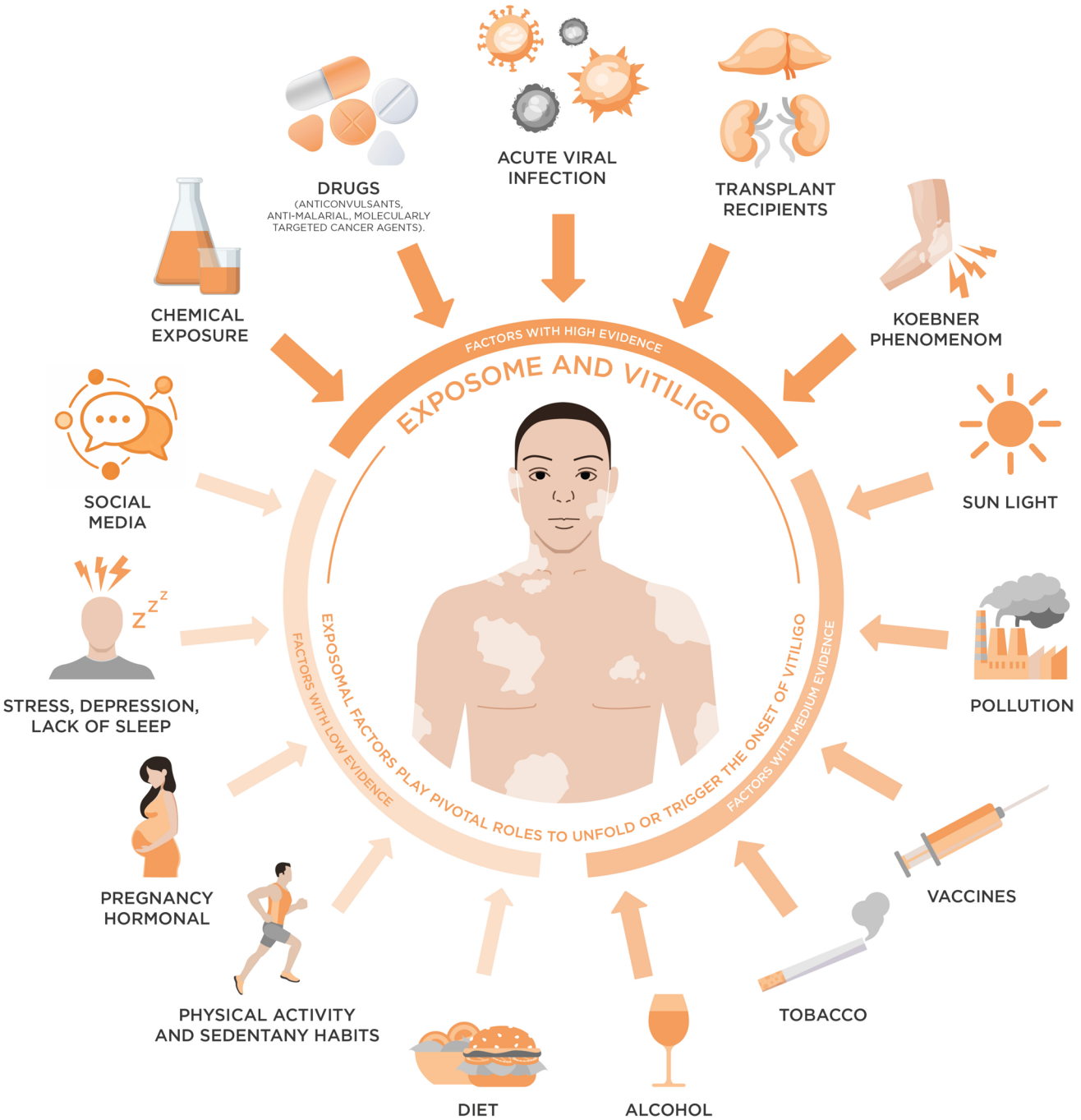

Fig. 3 The exposome as a trigger or modifier of vitiligo. Environmental and lifestyle factors, such as ultraviolet radiation, pollutants, trauma, transplantation, drugs, psychosocial stress, infections, hormonal changes, and social media, may contribute to vitiligo onset or progression with varying levels of evidence. This figure summarizes the main exposomal domains identified in the systematic review. Original illustration by the authors

standardized outcomes, making causal inference and generalizability difficult. Heterogeneity in study design and exposure definitions further complicates synthesis. Quantitative pooling was not feasible because of variability in data reporting and quality. Although heterogeneity of existing data precluded a formal meta-analysis, we mitigated this by classifying all associations into four evidence tiers of high consistency, moderate, emerging, and anecdotal, allowing a structured interpretation despite variable study designs. Only one reviewer screened each record and extracted data, representing a limitation relative to PRISMA 2020 guidance.

Despite these limitations, the findings have clinical relevance. Some exposures, particularly drugs, chemicals, and vaccines, are consistently associated with vitiligo and warrant discussion with patients, especially those with autoimmune predisposition. While complete avoidance is impractical, clinicians should offer guidance on modifiable triggers and promote protective strategies such as sun safety, chemical avoidance, and psychosocial support.

From a clinical standpoint, this evidence grading provides a pragmatic tool for patient counseling. High-consistency factors such as ICIs, phenolic chemicals, and recent infections warrant proactive discussion in clinical settings, while emerging factors such as sleep disturbance or diet may guide preventive research. This hierarchy bridges the gap between environmental risk recognition and actionable clinical guidance.

Evidence strength differs widely across exposomal factors. Strong associations exist for drugs (notably ICIs), phenolic chemicals, and COVID-19-related infection or vaccination. Stress, diet, smoking, and pollution show weaker or inconsistent signals, while graft-versus-host disease-related vitiligo remains plausible but diagnostically confounded. Other factors currently fall within anecdotal evidence.

5 Conclusions

Exposomal factors likely contribute to vitiligo onset and progression, though the strength of evidence varies considerably. Drug exposure, chemical agents, and recent vaccination show the most robust and replicated associations, while stress and lifestyle factors are less consistently supported and largely observational. Recognizing these differences is essential to avoid overinterpreting weak data and to better prioritize future research.

Well-designed longitudinal studies are needed to clarify causal links, improve risk stratification, and inform prevention strategies. In the meantime, clinicians should remain vigilant about high-risk exposures and provide evidence-informed guidance. While avoiding all triggers is unrealistic, mapping these exposures clarifies shared oxidative and immune pathways, offering a framework for prevention and hypothesis-driven research.

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Declarations

Conflicts of Interest/Competing Interests Jaime Piquero-Casals served as a speaker for Incyte Corporation and medical advisor for Isdin. Clémence Bertold received grants and/or honoraria from Novartis. Yolanda Gilaberte served as a consultant for Isdin, Cantabria Labs, Incyte, Almirall, UCB, and Leo Pharma, received research grants from Galderma, Almirall and Jansen, and provided lectures for Eucerin, Almirall, AbbVie, Cantabria Labs, Lilly, and Sanofi. José Luis López-Estebaranz served as a consultant, participated in clinical trials, and/or received speaking fees from Almirall, BMS, Janssen, Leo-Pharma, Lilly, AbbVie, Bioderma, Galderma, UCB, Novartis, Pierre-Fabre, Invasix, Isdin, and Incyte. Giovanni Leone has acted as a consultant for Isdin, AVITA Medical, Clinuvel, Incyte Corporation, and NAOS. Henry W. Lim has served as an investigator for Incyte, La Roche-Posay, Pfizer, and PCORI; a consultant for Isdin, Beiersdorf, Ferndale, L'Oréal, Eli Lilly, Zerigo Health, Cantabria Labs, and Skinosive; and as a speaker on general education sessions for La Roche-Posay, Cantabria Labs, Pierre Fabre, NAOS, Uriage, and Pfizer. Jean Krutmann serves as a consultant to Amway, bitop, Blue Lagoon, Evonik, ISDIN, La Roche-Posay, Mary Kay, Meitu, Mistine, Mibelle, Shin, Skinceuticals, Stada, Symrise, and Vichy, and IUF obtains funding from these organizations. Khaled Ezzedine has served as a consultant for and/or received grants from AbbVie, Almirall, Incyte, L'Oreal, La Roche Posay, Pfizer, Pierre Fabre, Sanofi, and Viela Bio. Thierry Passeron is a consultant for AbbVie, ACM Pharma, Almirall, Amgen, Beiersdorf, Bristol Myers Squibb, Calypso, Caudalie, Galderma, Incyte Corporation, ISDIN, Janssen, L'Oreal, Eli Lilly, Novartis, Pfizer, Roivant, SVR, Symrise, UCB, and VYNE Therapeutics. He has received grants and/or honoraria from AbbVie, ACM Pharma, Almirall, Amgen, Astellas, Beiersdorf, Bristol Myers Squibb, Calypso, Celgene, Galderma, Genzyme/Sanofi, GlaxoSmithKline, Incyte Corporation, Isdin, Isis Pharma, Janssen, LEO Pharma, Eli Lilly, Naos, Novartis, Pfizer, Roivant, Sun Pharmaceuticals, SVR, Takeda, UCB, and VYNE Therapeutics. He is the cofounder of NIKAIA Pharmaceuticals; and has patents on WNT agonists or GSK3b antagonist for repigmentation of vitiligo and the use of CXCR3B blockers in vitiligo. Agustín Alomar, Daniel Morgado-Carrasco, Antonio Massa, and Caio Silva de Castro have no conflicts of interest that are directly relevant to the content of this article.

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Authors and Affiliations

Jaime Piquero-Casals[1] · Clémence Bertold[2] · Agustín Alomar[3] · Daniel Morgado-Carrasco[4] · Yolanda Gilaberte[5] · José Luis López-Estebaranz[6] · Antonio Massa[7] · Caio Silva de Castro[8] · Giovanni Leone[9] · Henry W. Lim[10] · Jean Krutmann[11] · Khaled Ezzedine[12,13] · Thierry Passeron[2,14]

✉ Khaled Ezzedine

✉ Thierry Passeron
passeron@unice.fr

1 Department of Dermatology, Dermacentric Health & Aesthetics, Barcelona, Spain

2 Department of Dermatology, Centre Hospitalier Universitaire de Nice, Université Côte D'Azur, 150 route de St-Antoine de Ginetiere, 06200 Nice, France

3 Clinica Dermatologica Moragas, Barcelona, Spain

4 Department of Dermatology, Hospital Clinic de Barcelona, Barcelona, Spain

5 Department of Dermatology, Miguel Servet University Hospital, IIS Aragón, University of Zaragoza, Zaragoza, Spain

6 Dermatology Department, Hospital Universitario Fundación Alcorcón, Madrid, Spain

7 Clínica Dermatológica, Porto, Portugal

8 Hospital de Dermatologia Sanitária do Paraná, Piraquara, PR, Brazil

9 Photodermatology and Vitiligo Treatment Unit, Israelite Hospital, Rome, Italy

10 The Henry W. Lim Division of Photobiology and Photomedicine, Department of Dermatology, Henry Ford Health, Detroit, MI, USA

11 IUF, Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

12 Department of Dermatology, Henri Mondor University hospital, Créteil, France

13 Université Paris-Est Créteil, EpiDermE (Epidemiology in Dermatology and Evaluation of therapeutics), Institut Mondor de Recherche Biomédicale, Inserm U955, Université Paris Est Créteil (UPEC), Paris, France

14 Centre Méditerranéen de Médecine Moléculaire, INSERM U1065, Université Côte D'Azur, Nice, France