Dovepress

open access to scientific and medical research

R E V I E W

Association Between Atopic Dermatitis and Aging: Clinical Observations and Underlying Mechanisms

Peng-Yu Chen [ID][1], Minxue Shen [ID][2–4], Sui-Qing Cai [ID][1], Zhen-Wei Tang [ID][1]

[1]Department of Dermatology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, 310009, People's Republic of China; [2]Department of Dermatology, Xiangya Hospital, Central South University, Changsha, 410008, People's Republic of China; [3]Hunan Engineering Research Center of Skin Health and Disease; Hunan Key Laboratory of Skin Cancer and Psoriasis (Xiangya Hospital), Changsha, 410008, People's Republic of China; [4]Department of Social Medicine and Health Management, Xiangya School of Public Health, Central South University, Changsha, 410078, People's Republic of China

Correspondence: Zhen-Wei Tang; Sui-Qing Cai, Email tangzhenwei@zju.edu.cn; 2191008@zju.edu.cn

Abstract: As one of the most prevalent chronic inflammatory skin diseases, atopic dermatitis (AD) increasingly affects the aging population. Amid the ongoing global aging trend, it's essential to recognize the intricate relationship between AD and aging. This paper reviews existing knowledge, summarizing clinical observations of associations between AD and aging-related diseases in various systems, including endocrine, cardiovascular, and neurological. Additionally, it discusses major theories explaining the correlation, encompassing skin-mucosal barriers, systemic inflammation and stress, genes, signal transduction, and environmental and behavioral factors. The association between AD and aging holds significant importance, both in population and basic perspectives. While further research is warranted, this paper aims to inspire deeper exploration of inflammation/allergy-aging dynamics and the timely management of elderly patients with AD.

Keywords: atopic dermatitis, aging, age-related diseases, clinical observations, mechanical theories

Introduction

Overview of Atopic Dermatitis and Its Elderly Subtype

Atopic dermatitis (AD) stands as the predominant chronic inflammatory skin condition, representing a significant health burden among non-fatal skin diseases.[1] The onset and progression of AD are largely influenced by the complex interaction between environmental factors, neuro-immune responses, and skin barrier integrity.[2] Characterized by recurrent eczematous lesions and severe itching, AD significantly impairs quality of life.[1] Recognizing the variability in clinical manifestations across the lifespan, AD is traditionally divided into three age-based categories: infancy, childhood, and adolescence/adulthood. Recent empirical research has identified a distinct subtype of AD that affects the elderly, often manifesting lichenified eczema around the typically uninvolved flexural areas of the elbows and knees.[3,4] Dupilumab has shown rapid efficacy for this phenotype.[5] The distinctions between elderly AD and classic AD are elucidated in Table 1.

AD has seen a marked rise in global prevalence and incidence,[12] with up to 10% of adults affected.[13] Small-scale studies indicate significant international variation in AD prevalence among the elderly, ranging from 1.6% to 4%, and increasing with age.[1,14–19] However, it's crucial to note that the reported prevalence may underestimate the true impact, due to factors such as limited healthcare access for seniors, especially in underserved regions, and diagnostic challenges that can lead to AD being obscured or misdiagnosed.

3433

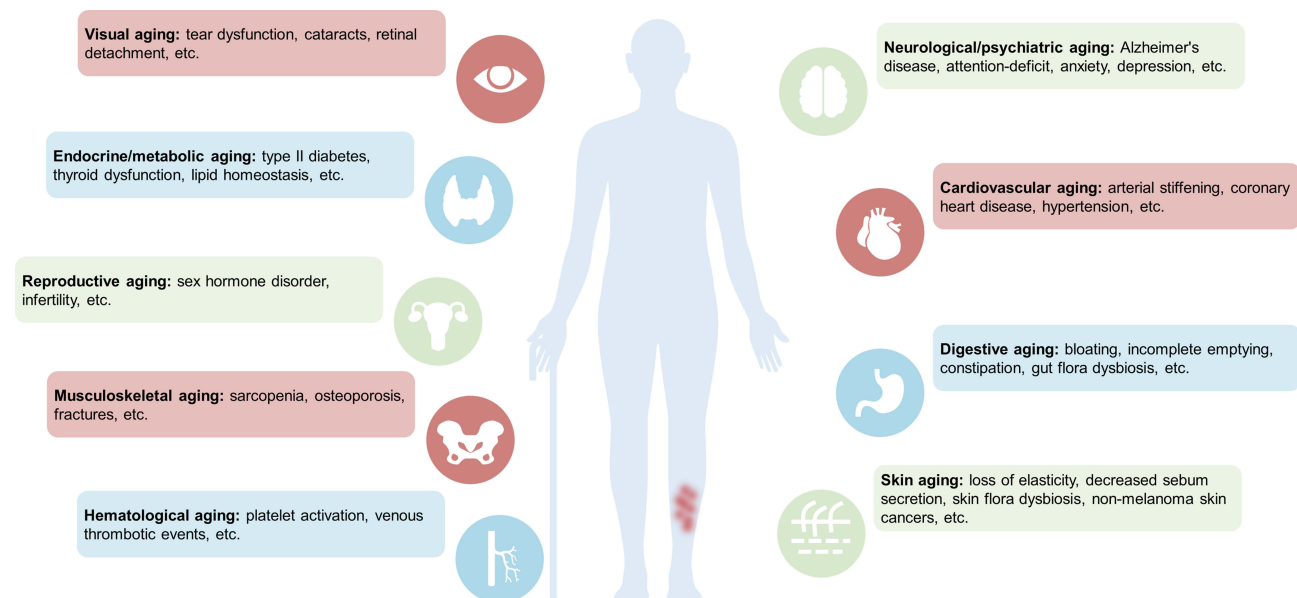**Table 1** The Differences Between Elderly AD and Classic AD

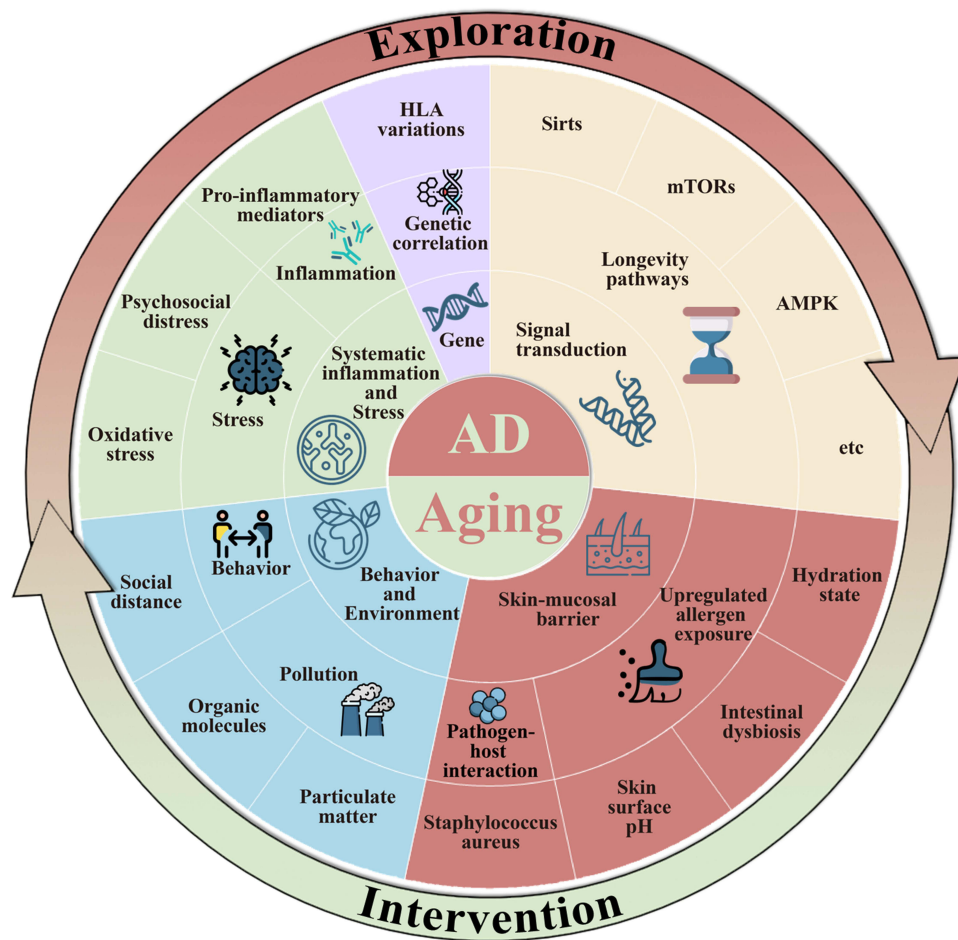|	Classic AD (Infant/Teenager)	Elderly AD
Pathogenesis	Th2 type inflammation predominant[6]	Bias toward mixed Th2/Th17/Th22 inflammation[7]
Rash	Acute or chronic eczema mainly on the head, face, and flexors of the extremities	Reverse symptoms of lichenified eczema around the extremities, back, etc.[3,8]
Endophenotype	Extrinsic AD (elevated total IgE levels and/or positive specific IgE) predominant	Intrinsic AD (normal total IgE levels and negative specific IgE) predominant[7]
Peripheral blood eosinophil count	Elevated	Normal or reduced[7]
Comorbidity	Atopic diseases such as allergic rhinitis, asthma, and food allergy	Cardiovascular,[9] psychiatric diseases,[10] Atopic diseases, osteoporosis,[11] etc

Association Between Aging and AD

Aging once deemed an inevitable aspect of the life cycle, is now understood to be a dynamic and modifiable biological process.[20] Globally, the population aged 65 and over is rising, with forecasts predicting a continued increase, surpassing 14% of the global population by 2040.[14] These demographic transformations present both opportunities and challenges for the study of age-related maladies and their biological foundations, a field that is already evolving and expected to grow.

AD demonstrates a biological connection with the aging process, evident in its disease profile. The research underscores the elevated prevalence of active AD among both children and the elderly,[12] possibly shifting primary AD care towards older demographics.[21,22] Subsequent investigations have uncovered unique immune responses in elderly AD sufferers, characterized by reduced serum IgE and eosinophil counts, and suggest links between AD and the aging of multiple systems, from both diseased and pre-diseased aspects.[7,18]

While these associations are apparent, a comprehensive synthesis of existing evidence is lacking. This narrative review consolidates clinical findings and foundational researches on AD and the aging process, utilizing a broad search across multiple databases and incorporating reverse citations up to September 2023. It summarizes recent clinical observations (Figure 1) and underlying mechanisms (Figure 2), aiming to clarify the relationship between AD and aging. However, it is important to note that narrative reviews may inherently lack an objective appraisal of the research evidence.

Visual aging: tear dysfunction, cataracts, retinal detachment, etc.

Neurological/psychiatric aging: Alzheimer's disease, attention-deficit, anxiety, depression, etc.

Endocrine/metabolic aging: type II diabetes, thyroid dysfunction, lipid homeostasis, etc.

Cardiovascular aging: arterial stiffening, coronary heart disease, hypertension, etc.

Reproductive aging: sex hormone disorder, infertility, etc.

Digestive aging: bloating, incomplete emptying, constipation, gut flora dysbiosis, etc.

Musculoskeletal aging: sarcopenia, osteoporosis, fractures, etc.

Skin aging: loss of elasticity, decreased sebum secretion, skin flora dysbiosis, non-melanoma skin cancers, etc.

Hematological aging: platelet activation, venous thrombotic events, etc.

Figure 1 Clinical observations of the possible relationship between AD and aging.

Figure 2 Potential mechanisms underlying the association between AD and aging.

Evidence from Clinical Observation

AD and Skin Aging

Skin aging, influenced by intrinsic factors like genetics and hormones, and extrinsic factors like ultraviolet radiation and pollutants, presents clinically with pigmentation changes, tissue atrophy, reduced elasticity, and impaired damage repair.[23] Additionally, it involves alterations in skin appendages, resulting in dryness and itching due to decreased sebum and sweat gland secretion.[24] Notably, aging also correlates with an increased incidence of non-melanoma skin cancers (NMSC).[25]

There is evidence linking skin aging, particularly in the elderly, to the development of AD. Age-related skin changes, such as a weakened skin barrier, increased colonization by *Staphylococcus aureus* (SA), innate immune system dysregulation, and pro-inflammatory type 2 T helper cell responses, may contribute to AD.[8] Researches show a positive correlation between AD severity and reduced skin lipid composition, including triglycerides, and decreased skin elasticity.[26–28] Patients with AD are also more susceptible to skin microbiome dysbiosis, characterized by increased SA and decreased *Staphylococcus epidermidis* (SE),[1,29,30] and bacteriotherapy may be beneficial.[30,31] Furthermore, AD may be associated with certain types of NMSC, possibly due to the chronic inflammatory state.[32] In summary, both AD and skin aging share immune response alterations, microflora changes, and reduced sebum content, and they tend to mutually reinforce each other.

AD and Cardiovascular Aging

Aging-related pathologies affecting the cardiovascular system primarily manifest as arterial stiffening, calcification, and myocardial cell function decline.[33] The aging process leads to arterial wall hardening, driven by an accumulation of

collagen and a loss of elastic proteins, possibly mediated by the expression of transforming growth factor-β and altered activity of elastic proteinases like matrix metalloproteinases (MMPs).[34] These pathological changes contribute to the development of essential hypertension and other cardiovascular diseases, including coronary heart disease.

The relationship between atopic dermatitis (AD) and cardiovascular diseases is a topic of active discussion, with a focus on whether systemic inflammation or traditional cardiovascular risk factors—such as obesity, smoking, and alcohol consumption—are the underlying links.[35–37] Studies that have accounted for these risk factors suggest that patients with AD do not have an inherently higher risk of cardiovascular diseases.[37–39] However, there is a stronger positive association with hypertension in cases of severe AD.[40] Moreover, foundational researches have identified elevated levels of cardiovascular risk biomarkers in patients with moderate to severe AD, indicating the potential presence of proteins, possibly skin-derived, that are upregulated in the bloodstream.[41–43] Recent US research, based on a nationally representative sample, has shown a correlation between coronary heart disease and AD, particularly in women and younger individuals, which may be associated with Th2 inflammation.[44] This suggests that previous studies with negative findings may not have adequately classified AD or its patient subgroups, resulting in an incomplete understanding of the cardiovascular risks exacerbated by AD-induced vascular inflammation. Therefore, the interplay between AD and cardiovascular aging requires continued and meticulous scrutiny and investigation.

AD and Hematological Aging

Aging profoundly impacts the hematological system, influencing immune system development, the microenvironment of hematopoietic stem cells, and the functionality of blood cells. It is commonly linked to decreased platelet counts and enhanced platelet reactivity, particularly in terms of aggregation.[45,46] Additionally, aging affects the coagulation system, predisposing individuals to a hypercoagulable state and raising the incidence of thrombotic conditions, such as venous thrombotic events (VTE).[47]

Research by Willeit et al has identified elevated levels of miRNA-24 and miRNA-191 in the plasma of patients with AD, which are associated with biomarkers of platelet activation.[48] Recent studies have also revealed a significantly heightened risk of VTE in patients who exhibit moderate to severe AD, are aged 45 and over, and do not have diabetes or use systemic corticosteroids.[49–51] In light of these findings, a more proactive screening and preventative approach to thrombosis may be warranted for elderly AD patients with additional risk factors for VTE, such as extended periods of immobility or the presence of malignancies.

AD and Endocrine/ Metabolic Aging

The aging process significantly affects the endocrine system, resulting in notable impacts on nutrient metabolism and hormonal fluctuations.

Aging impairs insulin secretion and blood glucose control by reducing the frequency and amplitude of insulin pulses and hindering the conversion of glucose to muscle glycogen.[52,53] The link between allergic diseases and blood glucose regulation has garnered attention. While epidemiological studies suggest an elevated risk of type II diabetes (T2D) in adults with AD,[54,55] this association is complex and not fully understood, with potential confounding factors such as age and glucocorticoid use needing further consideration.[56,57] A study that controlled for these factors found no significant differences in glucose metabolism between patients with AD and non-AD controls,[58] However, this study had limitations, involving only 16 young patients with mild to moderate AD, failing to demonstrate AD's impact on blood glucose fluctuations. Moreover, pathways associated with both complement and diabetes are reportedly more prevalent in adult AD.[59] Thus, AD may not directly affect glucose metabolism, but close monitoring of blood glucose in elderly patients with AD is a prudent precaution to detect potential metabolic changes linked to systemic inflammation.

Lipid metabolism is also impacted by aging, with increased levels of plasma LDL-C and total triglycerides observed, particularly in post-menopausal women.[60–64] In contrast, HDL-C levels remain relatively stable or slightly increase in elderly men but may decrease in post-menopausal women.[60,65] Recent research has identified an inverse correlation between triglyceride/LDL levels and AD, supported by Mendelian randomization.[66]

Age-related thyroid dysfunction is another area of concern, with a decline in serum T3 levels and a rise in TSH levels associated with an increased incidence of subclinical or overt hypothyroidism.[67–69] While research on the link

between AD and thyroid dysfunction in adults is limited, a study by Smith et al reported a significant association between the two, particularly in younger males, after accounting for potential confounders.[70] This connection may be due to shared immune dysregulation and cytokine pathways, and is further supported by overlapping genetic susceptibility loci.[71]

AD and Reproductive Aging

The maturation of the reproductive system marks the transition to puberty, while the aging process brings about a decline in reproductive function, including reduced sex hormones and fertility.[72] In males, aging often results in primary testicular failure, leading to lower androgen levels and a decrease in sperm count and quality.[73,74] Females experience a more rapid aging of the reproductive system,[75] which significantly impacts ovarian function, resulting in a decline in the number of oogonia and a reduction in estrogen levels.[76–79] Additionally, aging affects reproductive capacity and egg quality, with maternal age being a key determinant of pregnancy success and clinical outcomes.[80,81]

The association between sex hormones and AD has long intrigued researchers. Estrogen is believed to benefit the skin barrier and potentially alleviate AD, whereas progesterone and testosterone may exert negative effects.[82,83] However, findings from numerous studies on the link between AD and sex hormone levels are inconsistent[84–87] and have methodological limitations. For instance, the study by Vinnik et al may not be representative due to the selection of new-onset AD cases and the short duration of observation. Similarly, the population-based data from Kische et al may not accurately reflect the incidence, severity, or subtypes of AD. Future research should concentrate on life stages with significant hormonal changes, such as adolescence, pregnancy, and the menopausal transition. It should also consider subgroup analyses that account for both endogenous and exogenous factors, AD severity, and not just individual sex hormone levels but also receptor levels and sensitivity.[87,88] Alternatively, cytokines like IL-4 and IL-13 are known to stimulate the upregulation of 3β-hydroxysteroid dehydrogenase 1, which can promote androgen secretion in individuals with AD.[89] Furthermore, patients with AD often exhibit lower Vitamin D levels, which may be associated with hormonal fluctuations and reduced fertility.[90–93] A nationwide retrospective cohort study revealed that both mild and moderate-to-severe AD were significant risk factors for infertility.[94]

AD and Visual Aging

Aging significantly impacts the visual system, leading to an increased incidence of eye diseases, including tear dysfunction, age-related macular degeneration, cataracts, glaucoma, retinal detachment, and a general decline or loss of vision.[95–101] Patients with AD may experience premature aging of the visual system, which can manifest as tear film dysfunction and a heightened risk of spontaneous retinal detachment, potentially related to chronic eye rubbing and underlying connective tissue issues.[102–105] A study by Thyssen et al has identified a significant association between cataracts and individuals under 50 with both mild and severe AD.[106] For elderly individuals with AD, it may be thoughtful to closely monitor vision and overall eye health, particularly if they have facial or periocular involvement of AD.

AD and Digestive Aging

Digestive system aging is marked by a decline in digestive and absorptive efficiency, attributable to the degeneration of endogenous digestive enzymes,[107] alterations in endocrine hormone activity,[108] and atrophy of the small intestinal villi.[109] Additionally, age-related gastrointestinal motility disorders can precipitate difficulties in swallowing, gastro-esophageal reflux, constipation, and fecal incontinence, potentially linked to neural degeneration within the myenteric plexus of the gastrointestinal nervous system.[110] The gut microbiota also undergoes compositional changes, reflecting an ecological imbalance with a decrease in beneficial microorganisms like *Bifidobacteria* and a relative increase in potentially inflammatory bacteria, such as *Staphylococcaceae, Enterobacteriaceae*, and *Enterococcaceae*.[108,111]

Individuals with AD are more susceptible to gastrointestinal symptoms such as bloating, a sense of incomplete bowel emptying, and constipation.[112] The gut microbiota, a key regulator of the gut-skin axis, is integral to the interplay between AD and digestive health. Studies have shown that patients with AD often have a diminished diversity of gut

microbiota, with a reduction in beneficial bacteria like *Bifidobacterium* and a concurrent rise in SA,[113] mirroring changes observed with aging. Notably, Bifidobacterium's ability to metabolize indole derivatives may offer therapeutic potential for AD through the aryl hydrocarbon receptor signaling pathway.[114] This suggests that future research could benefit from exploring the specific metabolic pathways and metabolites of the gut microbiota to better understand the intricate dynamics among gut microbiota, AD, and the aging process.

AD and Musculoskeletal Aging

Aging has a profound impact on the musculoskeletal system, often resulting in skeletal muscle atrophy and metabolic imbalances of calcium and phosphate, which can lead to conditions such as sarcopenia and osteoporosis. These changes can manifest in negative health outcomes like fatigue, increased susceptibility to falls, and fractures.[115–117]

Recent research, encompassing observational studies and Mendelian randomization analysis, has shed light on the relationship between AD and sarcopenia.[118] Elderly patients with AD, especially those with longer disease duration, lower vitamin D levels, and systemic inflammation, face higher osteoporosis and fracture risks, recognized by the American Academy of Dermatology.[11,119–123] Hence, appropriate exercises programs, proactive osteoporosis intervention, and education on fall prevention might be considered essential for elderly patients with AD, whose benefits still require further research for substantiation.

AD and Neurological/Psychiatric Aging

Aging profoundly impacts the nervous system, leading to often irreversible neurological changes. This process results in a decline in cognitive abilities, emotional regulation, and autonomic function, which can negatively affect the quality of life, including social engagement, mental health, and physical performance.[124] Aging is also the leading risk factor for neurodegenerative diseases.[125–128] Furthermore, it also significantly influences the peripheral nervous system, particularly the cardiac and gastrointestinal components. Aging diminishes the ability of β-adrenergic stimulation to augment heart rate and cardiac output.[129] Age-related changes in the quantity and distribution of neurons in the gastrointestinal nervous plexus can lead to increased incidences of autonomic disorders such as arrhythmias and constipation.[130]

Patients with AD may experience a gradual decline in cognitive function, with an increased risk of developing dementia, especially Alzheimer's disease.[10,131] Childhood AD correlates with elevated rates of memory impairment, developmental delay, and attention-deficit/hyperactivity disorder.[132] Prospective and retrospective studies indicate that adult patients with AD are more prone to anxiety and depression, suggesting a possible bidirectional relationship between psychological distress and the severity of AD.[133,134] These observations underscore the complexity of psychological distress in elderly AD, necessitating further comprehensive research while considering confounding factors like social support, the level of national development, and gender differences.

Possible Mechanisms
Skin-Mucosal Barrier

Research on AD has highlighted the critical role of the skin and mucosal barriers. This barrier function intricately involves interactions among various innate and adaptive immune cells.[135] In AD, compromised epithelial cells release key cytokines such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25, which activate dendritic cells (DCs). These, in turn, prompt a type 2 immune response by stimulating Th2 cells and group 2 innate lymphoid cells (ILC2s).[136] This response involves a cascade of interactions among DCs, ILC2s, Th2 cells, and tissue cells, amplifying pathological immune reactions and further disrupting the skin barrier, perpetuating a detrimental cycle.[137] Specifically, Th2-derived cytokines like IL-4, IL-13, and IL-33 can impair the skin barrier by downregulating the expression of human beta-defensin (hBD)-3 and filaggrin, and by inhibiting the upregulation of tight junction proteins and hBD-2.[138] Additionally, the normally beneficial SE, which aids in ceramide synthesis and barrier maintenance, is less prevalent in individuals with AD.[139]

The integrity of the skin barrier is a focal point in dermatological research, particularly in the context of aging. With age, there is an increase in transepidermal water loss and a decrease in the integrity of the stratum corneum, along with a slower recovery from barrier disruption.[140,141] Aging also diminishes hydration of the stratum corneum and elevates skin surface pH due to decreased sebum and filaggrin, thereby increasing pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1a.[139,142–145] Additionally, aging promotes colonization by SA on the skin, which suppresses the expression of fatty acid elongase enzymes through the production of pro-inflammatory cytokines.[8,146] These age-related factors collectively weaken the skin barrier, triggering cytokine release that activates a type 2 immune response in epithelial cells.

Attention has also been drawn to the role of a compromised mucosal barrier in exacerbating inflammation by facilitating the entry of allergens and environmental factors. In the context of AD and aging, there is a growing interest in how intestinal dysbiosis can lead to mucosal barrier disruption and increased sensitivity to food allergens.[147,148] The gut microbiota from younger individuals has been shown to enhance the physical fitness of the elderly by altering skin gene expression, such as increasing the transcription of *Drebrin 1* (*Dbn1*), which aids in restoring barrier function.[148]

Systematic Inflammation and Stress

The link between allergic diseases, including AD, and aging is often explained by the concept of "inflammaging", which denotes a subtle, chronic, and low-grade inflammatory state associated with aging.[149] This state is characterized by a persistent activation of the innate immune system, leading to elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in the bloodstream.[150] Unlike the acute inflammation that serves as a protective response to infection or injury, chronic inflammation with age is implicated in the development of various diseases, including type 2 diabetes, cardiovascular disease, and neurodegenerative disorders.[20] Moderate to severe or poorly controlled AD often coincides with the similar chronically activated innate immune state,[151] heightening the risk of age-associated disease progression.

Stress is also a critical factor in aging, with acute yet non-lethal stressors like oxidative stress and DNA damage capable of inducing cellular senescence. This process triggers the release of signals that can cause nearby healthy cells to also become senescent, leading to a buildup of senescent cells and contributing to the aging process.[152] In AD, the compromised skin barrier increases the likelihood of allergens and environmental stressors affecting the skin, enhancing the production of reactive oxygen species and further fueling the chronic inflammation characteristic of AD, which can lead to cellular senescence.[153,154] Furthermore, senescent cells secrete a class of substances known as senescence-associated secretory phenotype, encompassing diverse cellular factors associated with AD.[155] Consequently, senescent cells themselves may partially contribute to AD progression.

At the individual level, stress refers to the body's response to new challenges—physical, emotional, or psychosocial—that disrupt homeostasis and trigger adaptive responses aimed at restoring balance.[156] Aging is generally thought to reduce the body's resilience to stressors, which can in turn accelerate the aging process.[157] Although AD is not typically life-threatening, it can cause significant stress due to chronic symptoms like itch-induced sleep disturbances, psychosocial challenges, and a tendency for relapses.[149,158] This chronic stress may increase the stress burden on an individual and could potentially accelerate the aging process.

Genes

Aging, age-related ailments, and AD, are complex traits that have been extensively studied through genome-wide association studies. Consequently, numerous susceptibility loci associated with these traits have been revealed, prompting geneticists to explore the role of these loci in trait expression.[159,160] For instance, as mentioned in Chapter 3.1, the gene *Dbn1* can enhance skin hydration and cognitive function, potentially offering protective effects against both AD and the aging process.[148]

Researchers have also used genomic association analysis to uncover shared susceptibility loci among different comorbidities, providing insights into why certain conditions often co-occur.[159,160] Recently, Zhou et al performed a comprehensive genome-wide linkage analysis for asthma, various cardiovascular diseases or traits, and pinpointed 145 overlapping susceptibility loci encompassing 99 genes linked to asthma and heart failure.[161] This finding suggests

a potential genetic link between asthma, AD, and other aging-related diseases, indicating a shared genetic predisposition. Additionally, AD has been observed to have a protective effect against dyslipidemia, which may be due to the unique genetic profile of individuals with allergic diseases.[66]

Variations in human leukocyte antigen (HLA) have been extensively proven to be significantly associated with allergic diseases.[162] Studies have suggested a correlation between *HLA-DR* expression and serum triglyceride levels, as well as a link between *HLA-DQB1* variations and lipid metabolism, which could influence longevity.[163,164] It is hypothesized that individuals with allergies may possess specific HLA variants that help maintain lipid balance and potentially extend life expectancy. Overall, future research may focus on genetically defining AD subtypes and elucidating the molecular mechanisms that underlie the genetic regulation of AD and aging traits, which could lead to more targeted and effective treatments.

Signal Transduction

Cellular functions are governed by complex molecular processes that are regulated through various signal transduction pathways. Recent progress in the fields of aging biology and immunology has highlighted how these interconnected pathways can impact both the aging process and the development of immunological diseases. Certain gene-related signal pathways have emerged as key regulators of aging and lifespan, including insulin-like growth factor-1, the target of rapamycin (TOR), AMP-activated protein kinase (AMPK), and Sirtuins.[33,165,166]

Researchers have found that the Sirtuin protein family, particularly Sirtuin6, influences the regulation of AMPK/ TOR and genome integrity.[33] Sirtuins, a class of histone deacetylases, consist of seven members with varying substrate affinity and subcellular localization.[167,168] An increase in Sirtuin6 expression is associated with improved repair of genomic damage and extended longevity in various species.[169] While the role of Sirtuins in AD is still under investigation, studies indicate reduced Sirtuin1 levels in AD. Epithelial-specific Sirtuin1 removal leads to AD-like skin issues, increased sensitivity to allergens, and reduced expression of the *Filaggrin* gene.[170] Additionally, MMP-1 expression induced by transient receptor potential vanilloid-1 (TRPV1) is crucial in skin aging and in the development of itch associated with histamine, IL-31, and TSLP.[166]

In summary, specific signal transduction pathways are likely to be essential in the interplay between AD and aging, potentially through their regulation of inflammation and disease progression.

Environment and Behavior

VCharacteristics of modern urban living and industrialization, such as increased night-time exposure to artificial light, air pollution, and a more sedentary lifestyle, are known to exacerbate atopic conditions, including AD.[171–174] These factors not only influence the incidence of AD but also potentially affect the aging process. A prominent example is particulate matter (PM), with epidemiological studies firmly establishing a link between PM exposure and AD incidence.[175] Experimental studies have demonstrated that PM2.5 exposure can compromise the skin barrier and provoke keratinocytes to release pro-inflammatory cytokines, thereby facilitating the onset of AD.[176,177] Additionally, the impact of PM on aging and aging-related diseases has gained attention. A study of 730 mother-infant pairs has shown that maternal exposure to PM2.5 during pregnancy correlates negatively with telomere length in neonatal cord blood and placental tissue.[178] PM-like particles have also been implicated in the development of age-related conditions such as dementia, cognitive decline, and hypertension,[179–181] suggesting a commonality of environmental risk factors between AD and aging.

Behavioral factors also elucidate the connection between AD, aging, and age-related diseases. Individuals with AD frequently face bullying, self-isolation, and difficulties in social interaction and forming close relationships.[182–184] These negative experiences can diminish social participation and lead to psychological and behavioral issues that are often associated with age-related diseases.[185–187] Consequently, AD may heighten susceptibility to age-related diseases through its impact on social behavior and mental health.

The mechanisms outlined above are visually summarized in Figure 3 for representation.
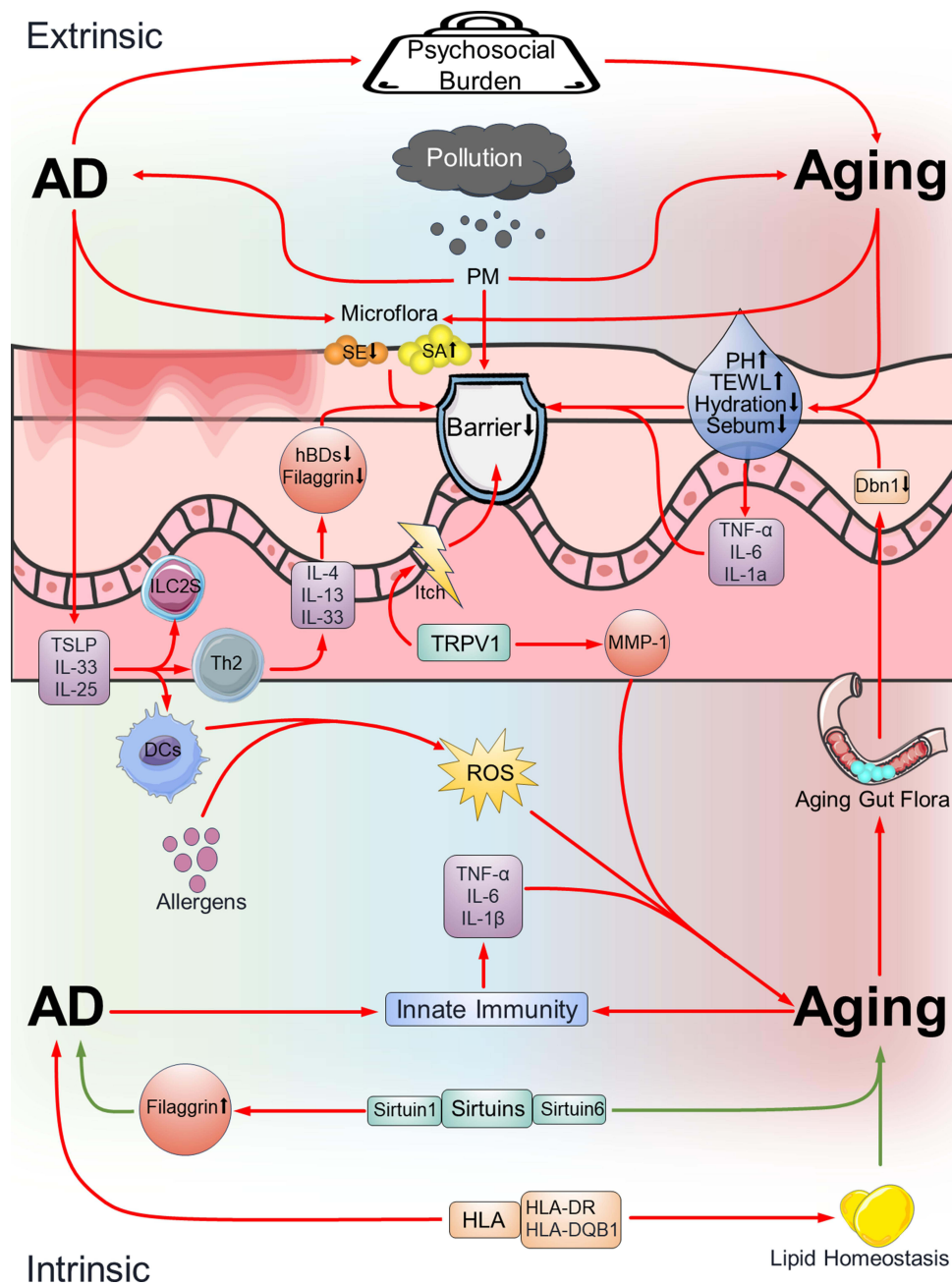
Figure 3 The network of representative mechanisms connecting AD and aging Red lines represent promotion, and green lines represent inhibition.
Abbreviations: AD, atopic dermatitis; PM, particulate matter; TEWL, transepidermal water loss; SA, Staphylococcus aureus; SE, Staphylococcus epidermidis; IL, interleukin; MMP, matrix metalloproteinase; TSLP, thymic stromal lymphopoietin; DCs, dendritic cells; ILC2s, activate group 2 innate lymphoid cells; hBDs, human beta-defensins; Dbn1, drebrin 1; ROS, reactive oxygen species; HLA, human leukocyte antigen; TRPV1, transient receptor potential vanilloid.

Conclusion

In conclusion, AD exhibits a positive correlation with aging and aging-related diseases in clinical practice, with exceptions such as the relationship between AD and dyslipidemia. While high-quality evidence for these associations is limited, some prospective cohort studies and Mendelian randomization analyses have begun to explore potential causal relationships. In the treatment of elderly patients with AD, it is crucial to consider both comorbid conditions and age-related factors.[188]

Mechanistically, the association between AD and aging is multifaceted, involving a complex interplay among various theories and forming a sophisticated regulatory network. Examining the relationship between AD and aging is significant,

whether from a population health or a basic science perspective. Firstly, a clear understanding of this association, particularly the element of causality, is essential for developing effective prevention and treatment strategies for AD in our aging population, thereby improving the health outcomes of older adults with AD. Secondly, insights into the underlying mechanisms can enhance our knowledge of the pathophysiology of both AD and aging, paving the way for more targeted interventions. Lastly, this review underscores the significant impact of chronic systemic inflammation, such as that seen in AD, which can accumulate and worsen with age. This realization encourages further research to improve the longevity and quality of life for all individuals.

Abbreviations

AD, atopic dermatitis; NMSC, non-melanoma skin cancers; MMP, matrix metalloproteinase; VTE, venous thrombotic events; T2D, type II diabetes; SA, Staphylococcus aureus; SE, Staphylococcus epidermidis; TSLP, thymic stromal lymphopoietin; DCs, dendritic cells; ILC2s, activate group 2 innate lymphoid cells; hBD, human beta-defensin; Dbn1, Drebrin 1; HLA, human leukocyte antigen; TOR, target of rapamycin; AMPK, AMP-activated protein kinase; TRPV1, transient receptor potential vanilloid 1; PM, particulate matter.

Acknowledgment

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Disclosure

The authors declare that they have no competing interests.

References

1. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet*. 2020;396(10247):345–360. doi:10.1016/S0140-6736(20)31286-1
2. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers*. 2018;4(1):1. doi:10.1038/s41572-018-0001-z
3. Bieber T, D'Erme AM, Akdis CA, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: where are we, and where should we go? *J Allergy Clin Immunol*. 2017;139(4s):S58–S64. doi:10.1016/j.jaci.2017.01.008
4. Tanei R, Hasegawa Y. Atopic dermatitis in older adults: a viewpoint from geriatric dermatology. *Geriatrics Gerontol Int*. 2016;16 Suppl 1 (S1):75–86. doi:10.1111/ggi.12771
5. Patruno C, Potestio L, Napolitano M. Clinical phenotypes of adult atopic dermatitis and related therapies. *Curr Opin Allergy Clin Immunol*. 2022;22(4):242–249. doi:10.1097/ACI.0000000000000837
6. Brunner PM, Israel A, Leonard A, et al. Distinct transcriptomic profiles of early-onset atopic dermatitis in blood and skin of pediatric patients. *Ann Allergy Asthma Immunol*. 2019;122(3):318–330.e313. doi:10.1016/j.anai.2018.11.025
7. Wang S, Zhu R, Gu C, et al. Distinct clinical features and serum cytokine pattern of elderly atopic dermatitis in China. *J Eur Acad Dermatol Venereol*. 2020;34(10):2346–2352. doi:10.1111/jdv.16346
8. Williamson S, Merritt J, De Benedetto A. Atopic dermatitis in the elderly: a review of clinical and pathophysiological hallmarks. *Br J Dermatol*. 2020;182(1):47–54. doi:10.1111/bjd.18652
9. Facheris P, Da Rosa JC, Pagan AD, et al. Age of onset defines two distinct profiles of atopic dermatitis in adults. *Allergy*. 2023;78 (8):2202–2214. doi:10.1111/all.15741
10. Pan TL, Bai YM, Cheng CM, et al. Atopic dermatitis and dementia risk: a nationwide longitudinal study. *Ann Allergy Asthma Immunol*. 2021;127(2):200–205. doi:10.1016/j.anai.2021.03.001

11. Kim S, Choi J, Cho MK, Kim NH, Kim SG, Kim KJ. Bone mineral density and osteoporosis risk in young adults with atopic dermatitis. *Sci Rep*. 2021;11(1):24228. doi:10.1038/s41598-021-03630-z

12. Shin YH, Hwang J, Kwon R, et al. Global, regional, and national burden of allergic disorders and their risk factors in 204 countries and territories, from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Allergy*. 2023;78(8):2232–2254. doi:10.1111/all.15807

13. Silverwood RJ, Mansfield KE, Mulick A, et al. Atopic eczema in adulthood and mortality: UK population-based cohort study, 1998–2016. *J Allergy Clin Immunol*. 2021;147(5):1753–1763. doi:10.1016/j.jaci.2020.12.001

14. Cauley JA. The demography of aging. In: Newman AB, Cauley JA, editors. *The Epidemiology of Aging*. Dordrecht: Springer Netherlands; 2012:3–14.

15. Wolkewitz M, Rothenbacher D, Löw M, et al. Lifetime prevalence of self-reported atopic diseases in a population-based sample of elderly subjects: results of the ESTHER study. *Br J Dermatol*. 2007;156(4):693–697. doi:10.1111/j.1365-2133.2006.07659.x

16. Bozek A, Fisher A, Filipowska B, Mazur B, Jarzab J. Clinical features and immunological markers of atopic dermatitis in elderly patients. *Int Arch Allergy Immunol*. 2012;157(4):372–378. doi:10.1159/000329150

17. Muto T, Hsieh SD, Sakurai Y, et al. Prevalence of atopic dermatitis in Japanese adults. *Br J Dermatol*. 2003;148(1):117–121. doi:10.1046/j.1365-2133.2003.05092.x

18. Chello C, Carnicelli G, Sernicola A, et al. Atopic dermatitis in the elderly Caucasian population: diagnostic clinical criteria and review of the literature. *Int J Dermatol*. 2020;59(6):716–721. doi:10.1111/ijd.14891

19. Ha J, Lee SW, Yon DK. Ten-year trends and prevalence of asthma, allergic rhinitis, and atopic dermatitis among the Korean population, 2008–2017. *Clin Experim Pediatr*. 2020;63(7):278–283. doi:10.3345/cep.2019.01291

20. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. *Nature*. 2019;571(7764):183–192. doi:10.1038/s41586-019-1365-2

21. Abuabara K, Magyari A, McCulloch CE, Linos E, Margolis DJ, Langan SM. Prevalence of atopic eczema among patients seen in primary care: data from the health improvement network. *Ann Internal Med*. 2019;170(5):354–356. doi:10.7326/M18-2246

22. Salava A, Rieppo R, Lauerma A, Salo V. Age-dependent distribution of atopic dermatitis in primary care: a nationwide population-based study from Finland. *Acta Derm Venereol*. 2022;102:adv00738. doi:10.2340/actadv.v102.2287

23. Kim JC, Park TJ, Kang HY. Skin-aging pigmentation: who is the real enemy? *Cells*. 2022;11(16). doi:10.3390/cells11162541

24. Zouboulis CC, Makrantonaki E. Clinical aspects and molecular diagnostics of skin aging. *Clin Dermatol*. 2011;29(1):3–14. doi:10.1016/j.clindermatol.2010.07.001

25. Khayyati Kohnehshahri M, Sarkesh A, Mohamed Khosroshahi L, et al. Current status of skin cancers with a focus on immunology and immunotherapy. *Can Cell Inter*. 2023;23(1):174. doi:10.1186/s12935-023-03012-7

26. Montero-Vilchez T, Cuenca-Barrales C, Rodriguez-Pozo JA, et al. Epidermal barrier function and skin homeostasis in atopic dermatitis: the impact of age. *Life*. 2022;12(1):132. doi:10.3390/life12010132

27. Yin H, Qiu Z, Zhu R, et al. Dysregulated lipidome of sebum in patients with atopic dermatitis. *Allergy*. 2022;78(6):1524–1537. doi:10.1111/all.15569

28. Eishi K, Lee JB, Bae SJ, Takenaka M, Katayama I. Impaired sweating function in adult atopic dermatitis: results of the quantitative sudomotor axon reflex test. *Br J Dermatol*. 2002;147(4):683–688. doi:10.1046/j.1365-2133.2002.04765.x

29. Fyhrquist N, Muirhead G, Prast-Nielsen S, et al. Microbe-host interplay in atopic dermatitis and psoriasis. *Nat Commun*. 2019;10(1):4703. doi:10.1038/s41467-019-12253-y

30. Nakatsuji T, Hata TR, Tong Y, et al. Development of a human skin commensal microbe for bacteriotherapy of atopic dermatitis and use in a Phase 1 randomized clinical trial. *Nature Med*. 2021;27(4):700–709. doi:10.1038/s41591-021-01256-2

31. Kim MS, Kim HJ, Kang SM, et al.. Efficacy and safety of topical Streptococcus postbiotic emollient in adolescents and adults with mild-to-moderate atopic dermatitis: a randomized, double-blind, vehicle-controlled trial. *Allergy*. 2024. doi:10.1111/all.16077

32. Ju T, Hernandez L, Mohsin N, Labib A, Frech F, Nouri K. Evaluation of risk in chronic cutaneous inflammatory conditions for malignant transformation. *J Eur Acad Dermatol Venereol*. 2023;37(2):231–242. doi:10.1111/jdv.18663

33. Masoro EJ. Austad SNJAoCN. *Handbook Biol Aging*. 2012;27:239–243.

34. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arteriosclerosis Thrombosis Vasc Biol*. 2005;25(5):932–943. doi:10.1161/01.ATV.0000160548.78317.29

35. Brunner PM, Silverberg JI, Guttman-Yassky E, et al. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. *J Investigat Dermatol*. 2017;137(1):18–25. doi:10.1016/j.jid.2016.08.022

36. Huang J, Gui Y, Wu J, Xie Y. Investigating the association of atopic dermatitis with ischemic stroke and coronary heart disease: a Mendelian randomization study. *Front Genetics*. 2022;13:956850. doi:10.3389/fgene.2022.956850

37. Ben Abdallah H, Vestergaard C. Atopic dermatitis, hypertension and cardiovascular disease. *Br J Dermatol*. 2022;186(2):203–204. doi:10.1111/bjd.20802

38. Drucker AM, Qureshi AA, Dummer TJB, Parker L, Li WQ. Atopic dermatitis and risk of hypertension, type 2 diabetes, myocardial infarction and stroke in a cross-sectional analysis from the Canadian Partnership for Tomorrow Project. *Br J Dermatol*. 2017;177(4):1043–1051. doi:10.1111/bjd.15727

39. Standl M, Tesch F, Baurecht H, et al. Association of atopic dermatitis with cardiovascular risk factors and diseases. *J Investigat Dermatol*. 2017;137(5):1074–1081. doi:10.1016/j.jid.2016.11.031

40. Yousaf M, Ayasse M, Ahmed A, et al. Association between atopic dermatitis and hypertension: a systematic review and meta-analysis. *Br J Dermatol*. 2022;186(2):227–235. doi:10.1111/bjd.20661

41. Pavel AB, Zhou L, Diaz A, et al. The proteomic skin profile of moderate-to-severe atopic dermatitis patients shows an inflammatory signature. *J Am Acad Dermatol*. 2020;82(3):690–699. doi:10.1016/j.jaad.2019.10.039

42. Glickman JW, Dubin C, Renert-Yuval Y, et al. Cross-sectional study of blood biomarkers of patients with moderate to severe alopecia areata reveals systemic immune and cardiovascular biomarker dysregulation. *J Am Acad Dermatol*. 2021;84(2):370–380. doi:10.1016/j.jaad.2020.04.138

43. Villani AP, Pavel AB, Wu J, et al. Vascular inflammation in moderate-to-severe atopic dermatitis is associated with enhanced Th2 response. *Allergy*. 2021;76(10):3107–3121. doi:10.1111/all.14859

44. Smith B, Engel P, Javadi SS, Han G, Wu JJ. Association between atopic dermatitis and cardiovascular disease in a nationally representative United States population. *J Am Acad Dermatol*. 2023;89(3):610–613.

45. Segal JB, Moliterno AR. Platelet counts differ by sex, ethnicity, and age in the United States. *Ann epidemiol*. 2006;16(2):123–130. doi:10.1016/j.annepidem.2005.06.052

46. Jones CI. Platelet function and ageing. *Mammalian Genome*. 2016;27(7–8):358–366. doi:10.1007/s00335-016-9629-8

47. Mari D, Coppola R, Provenzano R. Hemostasis factors and aging. *Exp Gerontology*. 2008;43(2):66–73. doi:10.1016/j.exger.2007.06.014

48. Willeit P, Zampetaki A, Dudek K, et al. Circulating microRNAs as novel biomarkers for platelet activation. *Circ Res*. 2013;112(4):595–600. doi:10.1161/CIRCRESAHA.111.300539

49. Hedderson MM, Asgari MM, Xu F, et al. Rates of cardiovascular events among patients with moderate-to-severe atopic dermatitis in an integrated health care system: a retrospective cohort study. *PLoS One*. 2022;17(11):e0277469. doi:10.1371/journal.pone.0277469

50. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985–2009). *Am j Med*. 2014;127(9):829–839.e825. doi:10.1016/j.amjmed.2014.03.041

51. Chen TL, Huang WT, Loh CH, Huang HK, Chi CC. Risk of venous thromboembolism among adults with atopic dermatitis. *JAMA Dermatol*. 2023;159(7):720. doi:10.1001/jamadermatol.2023.1300

52. van den Beld AW, Kaufman JM, Zillikens MC, Lamberts SWJ, Egan JM, van der Lely AJ. The physiology of endocrine systems with ageing. *Lancet Diabetes Endocrinol*. 2018;6(8):647–658. doi:10.1016/S2213-8587(18)30026-3

53. Broughton DL, Taylor R. Review: deterioration of glucose tolerance with age: the role of insulin resistance. *Age Ageing*. 1991;20(3):221–225. doi:10.1093/ageing/20.3.221

54. Thyssen JP, Linneberg A, Carlsen BC, et al. A possible association between a dysfunctional skin barrier (filaggrin null-mutation status) and diabetes: a cross-sectional study. *BMJ open*. 2011;1(1):e000062. doi:10.1136/bmjopen-2011-000062

55. Silverberg JI, Greenland P. Eczema and cardiovascular risk factors in 2 US adult population studies. *J Allergy Clin Immunol*. 2015;135(3):721–728.e726. doi:10.1016/j.jaci.2014.11.023

56. Andersen YMF, Egeberg A, Gislason GH, Skov L, Knop FK, Thyssen JP. Adult atopic dermatitis and the risk of type 2 diabetes. *J Allergy Clin Immunol*. 2017;139(3):1057–1059. doi:10.1016/j.jaci.2016.08.049

57. Thyssen JP, Halling-Overgaard AS, Andersen YMF, Gislason G, Skov L, Egeberg A. The association with cardiovascular disease and type 2 diabetes in adults with atopic dermatitis: a systematic review and meta-analysis. *Br J Dermatol*. 2018;178(6):1272–1279. doi:10.1111/bjd.16215

58. Gether L, Thyssen JP, Gyldenløve M, et al. Normal insulin sensitivity, glucose tolerance, gut incretin and pancreatic hormone responses in adults with atopic dermatitis. *Diabetes Obes Metab*. 2020;22(11):2161–2169. doi:10.1111/dom.14146

59. Del Duca E, Renert-Yuval Y, Pavel AB, et al. Proteomic characterization of atopic dermatitis blood from infancy to adulthood. *J Am Acad Dermatol*. 2023;88(5):1083–1093. doi:10.1016/j.jaad.2022.12.050

60. Liu HH, Li JJ. Aging and dyslipidemia: a review of potential mechanisms. *Ageing Res Rev*. 2015;19:43–52. doi:10.1016/j.arr.2014.12.001

61. Abbott RD, Garrison RJ, Wilson PW, et al. Joint distribution of lipoprotein cholesterol classes. The Framingham study. *Arteriosclerosis*. 1983;3(3):260–272. doi:10.1161/01.ATV.3.3.260

62. Ferrara A, Barrett-Connor E, Shan J. Total, LDL, and HDL cholesterol decrease with age in older men and women. The Rancho Bernardo Study 1984–1994. *Circulation*. 1997;96(1):37–43. doi:10.1161/01.CIR.96.1.37

63. Kreisberg RA, Kasim S. Cholesterol metabolism and aging. *Am j Med*. 1987;82(1b):54–60. doi:10.1016/0002-9343(87)90272-5

64. Gobal FA, Mehta JL. Management of dyslipidemia in the elderly population. *Therap Adv Cardiovasc Dis*. 2010;4(6):375–383. doi:10.1177/1753944710385048

65. Walter M. Interrelationships among HDL metabolism, aging, and atherosclerosis. *Arteriosclerosis Thrombosis Vasc Biol*. 2009;29(9):1244–1250. doi:10.1161/ATVBAHA.108.181438

66. Tang Z, Shen M, Xiao Y, Liu H, Chen X. Association between atopic dermatitis, asthma, and serum lipids: a UK biobank based observational study and Mendelian randomization analysis. *Front Med*. 2022;9:810092. doi:10.3389/fmed.2022.810092

67. Veldhuis JD. Changes in pituitary function with ageing and implications for patient care. *Nat Rev Endocrinol*. 2013;9(4):205–215. doi:10.1038/nrendo.2013.38

68. Boelaert K. Thyroid dysfunction in the elderly. *Nat Rev Endocrinol*. 2013;9(4):194–204. doi:10.1038/nrendo.2013.30

69. Duntas LH. Thyroid function in aging: a discerning approach. *Rejuvenation Res*. 2018;21(1):22–28. doi:10.1089/rej.2017.1991

70. Smith B, Collier MR, Devjani S, Han G, Wu JJ. Association between atopic dermatitis and thyroid disease among US adults in the 2001–2006 National Health and Nutrition Examination Survey. *J Am Acad Dermatol*. 2022;88(4):889–891. doi:10.1016/j.jaad.2022.10.017

71. Ellinghaus D, Baurecht H, Esparza-Gordillo J, et al. High-density genotyping study identifies four new susceptibility loci for atopic dermatitis. *Nature Genet*. 2013;45(7):808–812. doi:10.1038/ng.2642

72. Kaufman JM, Lapauw B, Mahmoud A, T'Sjoen G, Huhtaniemi IT. Aging and the male reproductive system. *Endocrine Reviews*. 2019;40(4):906–972. doi:10.1210/er.2018-00178

73. Gunes S, Hekim GN, Arslan MA, Asci R. Effects of aging on the male reproductive system. *J Assist Reprod Genet*. 2016;33(4):441–454. doi:10.1007/s10815-016-0663-y

74. Stone BA, Alex A, Werlin LB, Marrs RP. Age thresholds for changes in semen parameters in men. *Fertil Sterility*. 2013;100(4):952–958. doi:10.1016/j.fertnstert.2013.05.046

75. Moghadam ARE, Moghadam MT, Hemadi M, Saki G. Oocyte quality and aging. *JBRA Assist Reprod*. 2022;26(1):105–122. doi:10.5935/1518-0557.20210026

76. Broekmans FJ, Knauff EA, te Velde ER, Macklon NS, Fauser BC. Female reproductive ageing: current knowledge and future trends. *Trends Endocrinol Metab*. 2007;18(2):58–65. doi:10.1016/j.tem.2007.01.004

77. Markström E, Svensson E, Shao R, Svanberg B, Billig H. Survival factors regulating ovarian apoptosis – dependence on follicle differentiation. *Reproduction*. 2002;123(1):23–30. doi:10.1530/rep.0.1230023

78. Faddy MJ, Gosden RG. A model conforming the decline in follicle numbers to the age of menopause in women. *Hum Reprod*. 1996;11(7):1484–1486. doi:10.1093/oxfordjournals.humrep.a019422

79. te Velde ER, Pearson PL. The variability of female reproductive ageing. *Hum Reprod Update*. 2002;8(2):141–154. doi:10.1093/humupd/8.2.141

80. Wood JW. Fecundity and natural fertility in humans. *Oxford RevReprod Biol*. 1989;11:61–109.

81. Tan TY, Lau SK, Loh SF, Tan HH. Female ageing and reproductive outcome in assisted reproduction cycles. *Singapore Med J*. 2014;55 (6):305–309. doi:10.11622/smedj.2014081

82. Weare-Regales N, Chiarella SE, Cardet JC, Prakash YS, Lockey RF. Hormonal effects on asthma, rhinitis, and eczema. *J Allergy Clin Immunol Pract*. 2022;10(8):2066–2073. doi:10.1016/j.jaip.2022.04.002

83. Yuan W, Chen Y, Zhou Y, et al. Formononetin attenuates atopic dermatitis by upregulating A20 expression via activation of G protein-coupled estrogen receptor. *J Ethnopharmacol*. 2021;266:113397. doi:10.1016/j.jep.2020.113397

84. Ebata T, Itamura R, Aizawa H, Niimura M. Serum sex hormone levels in adult patients with atopic dermatitis. *J Dermatol*. 1996;23(9):603–605. doi:10.1111/j.1346-8138.1996.tb02662.x

85. Kasperska-Zajac A, Brzoza Z, Rogala B. Serum concentration of dehydroepiandrosterone sulfate and testosterone in women with severe atopic eczema/dermatitis syndrome. *J Invest Allergol Clin Immunol*. 2007;17(3):160–163.

86. Vinnik T, Kreinin A, Abildinova G, Batpenova G, Kirby M, Pinhasov A. Biological Sex and IgE Sensitization Influence Severity of Depression and Cortisol Levels in Atopic Dermatitis. *Dermatology*. 2020;236(4):336–344. doi:10.1159/000504388

87. Kische H, Hannemann A, Voss C, et al. Lack of significant association between sex hormone concentrations and atopic dermatitis in adolescents and adults in two population-based studies. *J Investigat Dermatol*. 2022;142(2):486–489.e484. doi:10.1016/j.jid.2021.07.133

88. Watanabe Y, Makino E, Tajiki-Nishino R, et al. Involvement of estrogen receptor α in pro-pruritic and pro-inflammatory responses in a mouse model of allergic dermatitis. *Toxicol Appl Pharmacol*. 2018;355:226–237. doi:10.1016/j.taap.2018.07.008

89. Zhang C, Chinnappan M, Prestwood CA, et al.. Interleukins 4 and 13 drive lipid abnormalities in skin cells through regulation of sex steroid hormone synthesis. *Proc Natl Acad Sci USA*. 2021;118(38):e2100749118.

90. Ng JC, Yew YW. Effect of vitamin D serum levels and supplementation on atopic dermatitis: a systematic review and meta-analysis. *Am J Clin Dermatol*. 2022;23(3):267–275. doi:10.1007/s40257-022-00677-0

91. Costanzo PR, Suárez SM, Kozak AE, Knoblovits P. Seasonal variations in sex steroids in a young male population and their relationship with plasma levels of vitamin D. *World J Mens Health*. 2022;40(2):308–315. doi:10.5534/wjmh.200156

92. Adamczewska D, Słowikowska-Hilczer J, Walczak-Jędrzejowska R. The association between vitamin D and the components of male fertility: a systematic review. *Biomedicines*. 2022;11(1):90. doi:10.3390/biomedicines11010090

93. Dupuis ML, Pagano MT, Pierdominici M, Ortona E. The role of vitamin D in autoimmune diseases: could sex make the difference? *Biol Sex Diff*. 2021;12(1):12. doi:10.1186/s13293-021-00358-3

94. Horev A, Shalom G, Weintraub AY, Freud T, Cohen AD. Atopic dermatitis and infertility: a nationwide retrospective cohort study. *Dermatology*. 2022;238(2):313–319. doi:10.1159/000515600

95. Weinberg J, Gaur M, Swaroop A, Taylor A. Proteostasis in aging-associated ocular disease. *Mol Aspect Med*. 2022;88:101157. doi:10.1016/j.mam.2022.101157

96. Burton MJ, Ramke J, Marques AP, et al. The lancet global health commission on global eye health: vision beyond 2020. *Lancet Glob Health*. 2021;9(4):e489–e551. doi:10.1016/S2214-109X(20)30488-5

97. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol*. 2004;122(4):477–485.

98. Hashemi H, Rastad H, Emamian MH, Fotouhi A. Meibomian gland dysfunction and its determinants in Iranian adults: a population-based study. *Contact Lens Anterior Eye*. 2017;40(4):213–216. doi:10.1016/j.clae.2017.05.003

99. Amano S, Inoue K. Clinic-based study on meibomian gland dysfunction in Japan. *Invest Ophthalmol Visual Sci*. 2017;58(2):1283–1287. doi:10.1167/iovs.16-21374

100. Steinmetz JD, Bourne RR, Briant PS, et al. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Health*. 2021;9(2):e144–e160. doi:10.1016/S2214-109X(20)30489-7

101. Varadaraj V, Ehrlich JR, Swenor BK. Vision impairment has implications for aging and health outcomes, beyond ophthalmology. *JAMA network open*. 2022;5(5):e2214610. doi:10.1001/jamanetworkopen.2022.14610

102. Beck KM, Seitzman GD, Yang EJ, Sanchez IM, Liao W. Ocular co-morbidities of atopic dermatitis. Part I: associated ocular diseases. *Am J Clin Dermatol*. 2019;20(6):797–805. doi:10.1007/s40257-019-00455-5

103. Oka C, Ideta H, Nagasaki H, Watanabe K, Shinagawa K. Retinal detachment with atopic dermatitis similar to traumatic retinal detachment. *Ophthalmology*. 1994;101(6):1050–1054. doi:10.1016/S0161-6420(94)31219-X

104. Taniguchi H, Ohki O, Yokozeki H, et al. Cataract and retinal detachment in patients with severe atopic dermatitis who were withdrawn from the use of topical corticosteroid. *J Dermatol*. 1999;26(10):658–665. doi:10.1111/j.1346-8138.1999.tb02068.x

105. Sy H, Bielory L. Atopic keratoconjunctivitis. *Allergy Asthma Proc*. 2013;34(1):33–41. doi:10.2500/aap.2013.34.3612

106. Thyssen JP, Toft PB, Halling-Overgaard AS, Gislason GH, Skov L, Egeberg A. Incidence, prevalence, and risk of selected ocular disease in adults with atopic dermatitis. *J Am Acad Dermatol*. 2017;77(2):280–286.e281. doi:10.1016/j.jaad.2017.03.003

107. Milan AM, Cameron-Smith D. Digestion and postprandial metabolism in the elderly. *Adv Food Nutr Res*. 2015;76:79–124. doi:10.1016/bs.afnr.2015.09.001

108. Lerner A, McCarty MF. The aging bowel dysfunction and elderly vulnerability towards COVID-19 infection. *Life*. 2021;11(2):97. doi:10.3390/life11020097

109. Soenen S, Rayner CK, Jones KL, Horowitz M. The ageing gastrointestinal tract. *Curr Opin Clin Nutr Metab Care*. 2016;19(1):12–18. doi:10.1097/MCO.0000000000000238

110. Nguyen VTT, Taheri N, Chandra A, Hayashi Y. Aging of enteric neuromuscular systems in gastrointestinal tract. *Neurogastroenterol Motil*. 2022;34(6):e14352. doi:10.1111/nmo.14352

111. Ragonnaud E, Biragyn A. Gut microbiota as the key controllers of "healthy" aging of elderly people. *Immunity Ageing*. 2021;18(1):2. doi:10.1186/s12979-020-00213-w

112. Islamoğlu ZG K, Unal M, Küçük A. Atopic dermatitis in adults and irritable bowel syndrome: a cross-sectional study. *Indian J Dermatol*. 2019;64(5):355–359. doi:10.4103/ijd.IJD_490_18

113. Zachariassen LF, Krych L, Engkilde K, et al. Sensitivity to oxazolone induced dermatitis is transferable with gut microbiota in mice. *Sci Rep*. 2017;7(1):44385. doi:10.1038/srep44385

114. Fang Z, Pan T, Li L, et al. Bifidobacterium longum mediated tryptophan metabolism to improve atopic dermatitis via the gut-skin axis. *Gut Microbes*. 2022;14(1):2044723. doi:10.1080/19490976.2022.2044723

115. Manolagas SC. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. *Endocrine Reviews*. 2010;31(3):266–300. doi:10.1210/er.2009-0024

116. Kassem M, Marie PJ. Senescence-associated intrinsic mechanisms of osteoblast dysfunctions. *Aging Cell*. 2011;10(2):191–197. doi:10.1111/j.1474-9726.2011.00669.x

117. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. *Lancet*. 2019;393(10191):2636–2646. doi:10.1016/S0140-6736(19)31138-9

118. Tang Z, Zhou G, Xiao Y, Liu H, Chen X, Shen M. Allergic phenotypes and sarcopenia: evidence from observational studies and Mendelian randomization analysis. *Phenomics*. 2023;4(1):46–50. doi:10.1007/s43657-023-00110-4

119. Shaheen MS, Silverberg JI. Atopic dermatitis is associated with osteoporosis and osteopenia in older adults. *J Am Acad Dermatol*. 2019;80 (2):550–551. doi:10.1016/j.jaad.2018.05.026

120. Lin TL, Wu CY, Yen JJ, et al. Fracture risks in patients with atopic dermatitis: a nationwide matched cohort study. *Ann Allergy Asthma Immunol*. 2021;127(6):667–673.e662. doi:10.1016/j.anai.2021.09.004

121. Thyssen JP, Halling AS, Schmid-Grendelmeier P, Guttman-Yassky E, Silverberg JI. Comorbidities of atopic dermatitis-what does the evidence say? *J Allergy Clin Immunol*. 2023;151(5):1155–1162. doi:10.1016/j.jaci.2022.12.002

122. Mukovozov IM, Morra DE, Giustini D, Tadrous M, Cheung AM, Drucker AM. Atopic dermatitis and bone health: a systematic review. *J Eur Acad Dermatol Venereol*. 2021;35(3):615–628. doi:10.1111/jdv.16895

123. Davis DMR, Drucker AM, Alikhan A, et al. American Academy of Dermatology Guidelines: awareness of comorbidities associated with atopic dermatitis in adults. *J Am Acad Dermatol*. 2022;86(6):1335–1336.e1318. doi:10.1016/j.jaad.2022.01.009

124. Satoh A, Imai SI, Guarente L. The brain, sirtuins, and ageing. *Nat Rev Neurosci*. 2017;18(6):362–374. doi:10.1038/nrn.2017.42

125. Page TL, Einstein M, Duan H, et al. Morphological alterations in neurons forming corticocortical projections in the neocortex of aged Patas monkeys. *Neurosci Lett*. 2002;317(1):37–41. doi:10.1016/S0304-3940(01)02428-4

126. Duan H, Wearne SL, Rocher AB, Macedo A, Morrison JH, Hof PR. Age-related dendritic and spine changes in corticocortically projecting neurons in macaque monkeys. *Cereb. Cortex*. 2003;13(9):950–961. doi:10.1093/cercor/13.9.950

127. Smith DE, Rapp PR, McKay HM, Roberts JA, Tuszynski MH. Memory impairment in aged primates is associated with focal death of cortical neurons and atrophy of subcortical neurons. *J Neurosci*. 2004;24(18):4373–4381. doi:10.1523/JNEUROSCI.4289-03.2004

128. Isaev NK, Stelmashook EV, Genrikhs EE. Neurogenesis and brain aging. *Rev Neurosci*. 2019;30(6):573–580. doi:10.1515/revneuro-2018-0084

129. Chadda KR, Ajijola OA, Vaseghi M, Shivkumar K, Huang CL, Jeevaratnam K. Ageing, the autonomic nervous system and arrhythmia: from brain to heart. *Ageing Res Rev*. 2018;48:40–50. doi:10.1016/j.arr.2018.09.005

130. Saffrey MJ. Cellular changes in the enteric nervous system during ageing. *Dev Biol*. 2013;382(1):344–355. doi:10.1016/j.ydbio.2013.03.015

131. Silverberg JI, Lei D, Yousaf M, et al. Association of atopic dermatitis severity with cognitive function in adults. *J Am Acad Dermatol*. 2020;83 (5):1349–1359. doi:10.1016/j.jaad.2020.05.041

132. Jackson-Cowan L, Cole EF, Silverberg JI, Lawley LP. Childhood atopic dermatitis is associated with cognitive dysfunction: a National Health Interview Survey study from 2008 to 2018. *Ann Allergy Asthma Immunol*. 2021;126(6):661–665. doi:10.1016/j.anai.2020.11.008

133. Birdi G, Larkin M, Knibb RC. Prospective analysis of the temporal relationship between psychological distress and atopic dermatitis in female adults: a preliminary study. *Healthcare*. 2022;10(10):1913. doi:10.3390/healthcare10101913

134. Roh YS, Huang AH, Sutaria N, et al. Real-world comorbidities of atopic dermatitis in the US adult ambulatory population. *J Am Acad Dermatol*. 2022;86(4):835–845. doi:10.1016/j.jaad.2021.11.014

135. Moens E, Veldhoen M. Epithelial barrier biology: good fences make good neighbours. *Immunology*. 2012;135(1):1–8. doi:10.1111/j.1365-2567.2011.03506.x

136. Celebi Sözener Z, Cevhertas L, Nadeau K, Akdis M, Akdis CA. Environmental factors in epithelial barrier dysfunction. *J Allergy Clin Immunol*. 2020;145(6):1517–1528. doi:10.1016/j.jaci.2020.04.024

137. Kuo IH, Yoshida T, De Benedetto A, Beck LA. The cutaneous innate immune response in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2013;131(2):266–278. doi:10.1016/j.jaci.2012.12.1563

138. Suwanchote S, Waitayangkoon P, Chancheewa B, et al. Role of antimicrobial peptides in atopic dermatitis. *Int J Dermatol*. 2022;61(5):532–540. doi:10.1111/ijd.15814

139. Zheng Y, Hunt RL, Villaruz AE, et al. Commensal Staphylococcus epidermidis contributes to skin barrier homeostasis by generating protective ceramides. *Cell Host Microbe*. 2022;30(3):301–313.e309. doi:10.1016/j.chom.2022.01.004

140. Lin ZC, Hsu CY, Hwang E, Wang PW, Fang JY. The role of cytokines/chemokines in an aging skin immune microenvironment. *Mech Ageing Dev*. 2023;210:111761. doi:10.1016/j.mad.2022.111761

141. Wang Z, Man MQ, Li T, Elias PM, Mauro TM. Aging-associated alterations in epidermal function and their clinical significance. *Aging*. 2020;12(6):5551–5565. doi:10.18632/aging.102946

142. Yang B, Lv C, Ye L, et al. Stratum corneum hydration inversely correlates with certain serum cytokine levels in the elderly, possibly contributing to inflammaging. *Immunity Ageing*. 2023;20(1):7. doi:10.1186/s12979-023-00331-1

143. Man MQ, Xin SJ, Song SP, et al. Variation of skin surface pH, sebum content and stratum corneum hydration with age and gender in a large Chinese population. *Skin Pharmacol Physiol*. 2009;22(4):190–199. doi:10.1159/000231524

144. Choi EH, Man MQ, Xu P, et al. Stratum corneum acidification is impaired in moderately aged human and murine skin. *J Investigat Dermatol*. 2007;127(12):2847–2856. doi:10.1038/sj.jid.5700913

145. Vávrová K, Henkes D, Strüver K, et al. Filaggrin deficiency leads to impaired lipid profile and altered acidification pathways in a 3D skin construct. *J Investigat Dermatol*. 2014;134(3):746–753. doi:10.1038/jid.2013.402

146. Kim J, Kim BE, Berdyshev E, et al. Staphylococcus aureus causes aberrant epidermal lipid composition and skin barrier dysfunction. *Allergy*. 2023;78(5):1292–1306. doi:10.1111/all.15640

147. Zhu TH, Zhu TR, Tran KA, Sivamani RK, Shi VY. Epithelial barrier dysfunctions in atopic dermatitis: a skin-gut-lung model linking microbiome alteration and immune dysregulation. *Br J Dermatol*. 2018;179(3):570–581. doi:10.1111/bjd.16734

148. Kim KH, Chung Y, Huh JW, et al. Gut microbiota of the young ameliorates physical fitness of the aged in mice. *Microbiome*. 2022;10(1):238. doi:10.1186/s40168-022-01386-w

149. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908 (1):244–254. doi:10.1111/j.1749-6632.2000.tb06651.x

150. Liberale L, Montecucco F, Tardif JC, Libby P, Camici GG. Inflamm-ageing: the role of inflammation in age-dependent cardiovascular disease. *Eur Heart J*. 2020;41(31):2974–2982. doi:10.1093/eurheartj/ehz961

151. Ong PY. Atopic dermatitis: is innate or adaptive immunity in control? A clinical perspective. *Front Immunol*. 2022;13:943640. doi:10.3389/fimmu.2022.943640

152. de Magalhães JP, Passos JF. Stress, cell senescence and organismal ageing. *Mech Ageing Dev*. 2018;170:2–9. doi:10.1016/j.mad.2017.07.001

153. Sánchez A, Calpena AC, Clares B. Evaluating the oxidative stress in inflammation: role of melatonin. *Int J Mol Sci*. 2015;16(8):16981–17004. doi:10.3390/ijms160816981

154. Wang ZN, Su RN, Yang BY, et al. Potential role of cellular senescence in asthma. *Front Cell Develop Biol*. 2020;8:59. doi:10.3389/fcell.2020.00059

155. Coppé JP, Patil CK, Rodier F, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS biol*. 2008;6(12):2853–2868. doi:10.1371/journal.pbio.0060301

156. Pardon MC. Stress and ageing interactions: a paradox in the context of shared etiological and physiopathological processes. *Brain Res Rev*. 2007;54(2):251–273. doi:10.1016/j.brainresrev.2007.02.007

157. Vitlic A, Lord JM, Phillips AC. Stress, ageing and their influence on functional, cellular and molecular aspects of the immune system. *Age*. 2014;36(3):9631. doi:10.1007/s11357-014-9631-6

158. Lin TK, Zhong L, Santiago JL. Association between stress and the HPA axis in the atopic dermatitis. *Int J Mol Sci*. 2017;18(10):2131. doi:10.3390/ijms18102131

159. Bahrami S, Steen NE, Shadrin A, et al. Shared genetic loci between body mass index and major psychiatric disorders: a genome-wide association study. *JAMA psychiatry*. 2020;77(5):503–512. doi:10.1001/jamapsychiatry.2019.4188

160. Bahrami S, Shadrin A, Frei O, et al. Genetic loci shared between major depression and intelligence with mixed directions of effect. *Nat Human Behav*. 2021;5(6):795–801. doi:10.1038/s41562-020-01031-2

161. Zhou Y, Liang ZS, Jin Y, et al. Shared genetic architecture and causal relationship between asthma and cardiovascular diseases: a large-scale cross-trait analysis. *Front Genetics*. 2021;12:775591. doi:10.3389/fgene.2021.775591

162. Schoettler N, Rodríguez E, Weidinger S, Ober C. Advances in asthma and allergic disease genetics: is bigger always better? *J Allergy Clin Immunol*. 2019;144(6):1495–1506. doi:10.1016/j.jaci.2019.10.023

163. Restrepo BI, Twahirwa M, Jagannath C. Hyperglycemia and dyslipidemia: reduced HLA-DR expression in monocyte subpopulations from diabetes patients. *Hum Immunol*. 2021;82(2):124–129. doi:10.1016/j.humimm.2020.11.005

164. Yang F, Sun L, Zhu X, et al. Identification of new genetic variants of HLA-DQB1 associated with human longevity and lipid homeostasis-a cross-sectional study in a Chinese population. *Aging*. 2017;9(11):2316–2333. doi:10.18632/aging.101323

165. Guarente L, Kenyon C. Genetic pathways that regulate ageing in model organisms. *Nature*. 2000;408(6809):255–262. doi:10.1038/35041700

166. Xiao T, Sun M, Zhao C, Kang J. TRPV1: a promising therapeutic target for skin aging and inflammatory skin diseases. *Front Pharmacol*. 2023;14:1037925. doi:10.3389/fphar.2023.1037925

167. Schemies J, Uciechowska U, Sippl W, Jung M. NAD(+) -dependent histone deacetylases (sirtuins) as novel therapeutic targets. *Med Res Rev*. 2010;30(6):861–889. doi:10.1002/med.20178

168. Vassilopoulos A, Fritz KS, Petersen DR, Gius D. The human sirtuin family: evolutionary divergences and functions. *Hum Genomics*. 2011;5 (5):485–496. doi:10.1186/1479-7364-5-5-485

169. Tian X, Firsanov D, Zhang Z, et al. SIRT6 is responsible for more efficient DNA double-strand break repair in long-lived species. *Cell*. 2019;177(3):622–638.e622. doi:10.1016/j.cell.2019.03.043

170. Ming M, Zhao B, Shea CR, et al. Loss of sirtuin 1 (SIRT1) disrupts skin barrier integrity and sensitizes mice to epicutaneous allergen challenge. *J Allergy Clin Immunol*. 2015;135(4):936–945.e934. doi:10.1016/j.jaci.2014.09.035

171. Murrison LB, Brandt EB, Myers JB, Hershey GKK. Environmental exposures and mechanisms in allergy and asthma development. *J Clin Invest*. 2019;129(4):1504–1515. doi:10.1172/JCI124612

172. Tang Z, Li S, Shen M, et al. Association of exposure to artificial light at night with atopic diseases: a cross-sectional study in college students. *Int J Hygiene Environ Health*. 2022;241:113932. doi:10.1016/j.ijheh.2022.113932

173. Mahdavinia M, Greenfield LR, Moore D, et al. House dust microbiota and atopic dermatitis; effect of urbanization. *Pediatr Allergy Immunol*. 2021;32(5):1006–1012. doi:10.1111/pai.13471

174. Weinberg EG. Urbanization and childhood asthma: an African perspective. *J Allergy Clin Immunol*. 2000;105(2 Pt 1):224–231. doi:10.1016/S0091-6749(00)90069-1

175. Ngoc LTN, Park D, Lee Y, Lee YC. Systematic review and meta-analysis of human skin diseases due to particulate matter. *Int J Environ Res Public Health*. 2017;14(12):1458. doi:10.3390/ijerph14121458

176. Li F, Dong Y, Ni C, Kan H, Yan S. Fine Particulate Matter (PM2.5) is a risk factor for dermatitis by promoting the expression of Thymic Stromal Lymphopoietin (TSLP) in keratinocytes. *Indian J Dermatol*. 2020;65(2):92–96. doi:10.4103/ijd.IJD_520_18

177. Kim BE, Kim J, Goleva E, et al.. Particulate matter causes skin barrier dysfunction. *JCI Insight*. 2021;6(5). doi:10.1172/jci.insight.145185

178. Martens DS, Cox B, Janssen BG, et al. Prenatal air pollution and newborns' predisposition to accelerated biological aging. *JAMA Pediatr*. 2017;171(12):1160–1167. doi:10.1001/jamapediatrics.2017.3024

179. Grande G, Ljungman PLS, Eneroth K, Bellander T, Rizzuto D. Association between cardiovascular disease and long-term exposure to air pollution with the risk of dementia. *JAMA neurol*. 2020;77(7):801–809. doi:10.1001/jamaneurol.2019.4914

180. Younan D, Petkus AJ, Widaman KF, et al. Particulate matter and episodic memory decline mediated by early neuroanatomic biomarkers of Alzheimer's disease. *Brain*. 2020;143(1):289–302.

181. Wu Y, Ye Z, Fang Y. Spatial analysis of the effects of PM2.5 on hypertension among the middle-aged and elderly people in China. *Int J Environ Health Res*. 2021;31(6):729–740.

182. Marron SE, Cebrian-Rodriguez J, Alcalde-Herrero VM, Garcia-latasa de Aranibar FJ, Tomas-Aragones L. Psychosocial impact of atopic dermatitis in adults: a qualitative study. *Actas Dermo-Sifiliograficas*. 2020;111(6):513–517. doi:10.1016/j.ad.2019.03.018

183. Chamlin SL, Frieden IJ, Williams ML, Chren MM. Effects of atopic dermatitis on young American children and their families. *Pediatrics*. 2004;114(3):607–611. doi:10.1542/peds.2004-0374

184. Stingeni L, Belloni Fortina A, Baiardini I, Hansel K, Moretti D, Cipriani F. Atopic dermatitis and patient perspectives: insights of bullying at school and career discrimination at work. *J Asthma Allergy*. 2021;14:919–928. doi:10.2147/JAA.S317009

185. Evans IEM, Martyr A, Collins R, Brayne C, Clare L. Social Isolation and Cognitive Function in Later Life: a Systematic Review and Meta-Analysis. *J Alzheimers Dis*. 2019;70(s1):S119–S144. doi:10.3233/JAD-180501

186. Penninkilampi R, Casey AN, Singh MF, Brodaty H. The association between social engagement, loneliness, and risk of dementia: a systematic review and meta-analysis. *J Alzheimers Dis*. 2018;66(4):1619–1633. doi:10.3233/JAD-180439

187. Valtorta NK, Kanaan M, Gilbody S, Hanratty B. Loneliness, social isolation and risk of cardiovascular disease in the English Longitudinal Study of Ageing. *Eur J Prevent Cardiol*. 2018;25(13):1387–1396. doi:10.1177/2047487318792696

188. Napolitano M, Potestio L, Nocerino M, Patruno C. Considerations for managing elderly patients with atopic dermatitis. *Expert Rev Clin Immunol*. 2024;20(5):501–511. doi:10.1080/1744666X.2024.2301967