***Review***

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# The skin as a sentinel organ for neurodegeneration: An underrecognized target for dementia prevention

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**SUMMARY**: Dementia prevention increasingly requires attention to modifiable systemic inflammatory stressors. In older adults, bullous pemphigoid (BP), herpes zoster (HZ), psoriasis, atopic dermatitis (AD), rosacea, prurigo nodularis (PN), and chronic pruritus are not merely disorders limited to the skin; they may signal or amplify neuroimmune vulnerability. Observational studies link BP with dementia and Alzheimer's disease, HZ with incident dementia and vascular cognitive injury, and psoriasis, AD, rosacea, or PN with smaller but biologically plausible cognitive risks. The proposed skin-brain axis integrates cytokine spillover, endothelial activation, blood-brain barrier dysfunction, BP180/BP230 autoantigen sharing, varicella-zoster virus neurotropism and vasculopathy, barrier failure, dysbiosis, itching-induced fragmented sleep, and medication or frailty-related cognitive toxicity. Clinically, cognitive impairment also worsens skin surveillance, hygiene, topical adherence, and recognition of pain, itching, infection, or blistering. Although causality and dementia prevention remain unproven, the evidence justifies proactive dermatological care in older adults and greater cognitive vigilance in older patients with severe inflammatory or pruritic dermatoses. Recombinant zoster vaccination, prompt antiviral therapy, steroid-sparing BP strategies, modern anti-inflammatory treatment for AD, psoriasis, and PN, and systematic attention to sleep, itching, caregiver capacity, and the medication burden are practical, low-regret steps while prospective brain-relevant trials are developed. This translational framework highlights mechanisms clinicians can now interrupt and endpoints investigators can soon measure. We propose that the skin should be recognized as a sentinel organ for neurodegeneration and that dermatological disease represents a potentially modifiable contributor to cognitive decline.

***Keywords***: dementia, skin-brain axis, bullous pemphigoid, herpes zoster, psoriasis, atopic dermatitis, rosacea, prurigo nodularis

## 1. Introduction

Population aging has made dementia a defining public-health and geriatric-care challenge. The World Health Organization estimates that the number of adults age 60 years and older will increase from 1.0 billion in 2020 to 1.4 billion in 2030 and 2.1 billion in 2050, while the population age 80 years or older is projected to triple to 426 million over the same period (*1,2*). Dementia is expanding in parallel: an estimated 57 million people were living with dementia worldwide in 2021, more than 60% of whom were living in low- and middle-income countries, and Global Burden of Disease forecasting suggests that this number may reach 152.8 million by 2050 (*3,4*). These trends have shifted dementia prevention away from a narrow focus on late-stage neurodegeneration toward cumulative, modifiable stresses across a person's life course. In addition to vascular, metabolic, sensory, and lifestyle risks, prevention frameworks increasingly need to account for peripheral inflammation, infection, sleep disruption, medication toxicity, frailty, and other systemic stressors that may erode cognitive reserve before dementia is clinically established.

The skin is a distinctive entry point into this broader prevention framework because it is visible, accessible, immune-active, and continuously exposed to environmental, microbial, inflammatory, vascular, and neural signals. Aging skin is characterized by impaired barrier repair, xerosis, dysregulated immunity, sensory dysfunction, vascular fragility, and slower wound healing, while cognitive impairment reduces the ability to recognize itching, pain, infection, blistering, adverse effects of medication, or early skin breakdown and it

limits adherence to topical regimens (*5-7*). However, the skin should be considered not only a vulnerable target in dementia care, but also a potential sentinel organ for dementia-related biology. Chronic inflammatory, infectious, autoimmune, and pruritic skin diseases may reveal systemic immune activation, neurovascular stress, fragmented sleep, pain, itching, and frailty-related vulnerability in ways that are directly observable in routine dermatological practice.

This review focuses on inflammatory, autoimmune, infectious, and pruritic dermatoses with emerging dementia-related signals, including bullous pemphigoid (BP), herpes zoster (HZ), psoriasis, atopic dermatitis (AD), rosacea, prurigo nodularis (PN), and chronic pruritus. The strength and directionality of evidence differ substantially across these conditions. BP and HZ currently provide the most distinctive disease-specific signals: BP because of its strong association with dementia and biologically plausible BP180/BP230-related neurocutaneous autoimmunity, and HZ because varicella-zoster virus neurotropism, vasculopathy, antiviral treatment, and zoster vaccination create a temporally discrete and potentially preventable neurocutaneous model. In contrast, psoriasis, AD, rosacea, PN, and chronic pruritus offer more modest, heterogeneous, or hypothesis-generating evidence, although their links with systemic inflammation, itching, sleep loss, a mood disturbance, vascular comorbidity, and the treatment burden remain clinically important.

We have organized the evidence into three clinically testable axes linking skin disease and cognitive vulnerability: neuroinflammation, neurovascular injury, and neurofunctional disruption. The neuroinflammatory axis integrates cytokine spillover, endothelial activation, blood-brain barrier vulnerability, microglial and astrocytic priming, and BP-related autoantigen sharing. The neurovascular axis emphasizes HZ/varicella-zoster virus (VZV)-related vasculopathy, endothelial injury, thrombosis, ischemic burden, and vascular cognitive impairment. The neurofunctional axis captures itching, pain, fragmented sleep, sedating or anticholinergic medication exposure, corticosteroid toxicity, infection, frailty, delirium risk, and caregiver-dependent treatment failure. This framework does not assume that treating a skin disease prevents dementia. Rather, it proposes that a dermatological disease can provide visible, modifiable, and research-ready signals through which dermatologists, geriatricians, neurologists, and primary-care clinicians can identify cognitive vulnerability earlier, they can reduce low-regret contributors to brain stress, and they can design prospective studies with brain-related endpoints.

## 2. Why this issue deserves attention

Dementia is a dominant challenge of population aging, and current prevention frameworks emphasize management of cumulative vascular, inflammatory, sensory, sleep, and lifestyle risks (*8,9*). At the same time, inflammatory and pruritic dermatoses are common in later life, frequently undertreated in frail patients, and often dismissed as problems of comfort or appearance. This separation is increasingly untenable. A skin-brain axis model proposes bidirectional communication: chronic cutaneous inflammation may contribute to systemic and central neuroimmune activation, whereas cognitive decline impairs barrier care, scratching control, hygiene, treatment adherence, and timely reporting of early blistering, pain, infection, or itching (*10*).

## 3. Clinical and interventional signals linking skin disease and cognition

The strongest dermatological signal currently comes from BP, a prototypic inflammatory blistering disorder of late life. A systematic review and meta-analysis found that BP is associated with adverse cognitive outcomes, and observational studies have repeatedly reported increased antecedent dementia in BP cohorts (*11,12*). Mechanistic plausibility is strengthened by evidence that BP180-related autoimmunity may intersect with neuronal tissue, with higher BP180 autoantibody levels reported in patients with Alzheimer's disease and distinct central nervous system (CNS)-related epitope recognition patterns described in neurodegenerative disease (*13,14*). Given that BP also causes severe itching, skin breakdown, sleep disruption, infection risk, and corticosteroid exposure, it is a plausible amplifier of cognitive vulnerability in patients who are already frail. Table 1 summarizes the major clinicopathologic associations.

Beyond epidemiologic overlap, the BP–dementia signal is biologically unusual because BP180/collagen XVII and BP230/dystonin have neuronal isoforms. In Alzheimer's disease, higher serum BP180 autoantibody levels correlate with more severe dementia, and the epitopes recognized in Alzheimer's disease or multiple sclerosis differ from those typically seen in cutaneous BP, suggesting epitope-specific neurocutaneous immunity rather than simple bystander seropositivity (*15,16*). This pattern is consistent with a bidirectional model in which neurodegeneration may expose neural BP antigens and prime autoimmunity, while systemic autoantibody and complement activation sustain a frailty-promoting inflammatory state.

HZ provides a second compelling example. Population-based studies suggest that incident HZ, and particularly when the central nervous system is involved, is associated with a higher risk of subsequent dementia, while antiviral treatment may attenuate this association (*17,18*). Even more provocative are recent vaccine studies showing that zoster vaccination is associated with a lower incidence or delayed diagnosis

**Table 1. Associations between skin diseases and cognitive impairment**

| Skin disease | Associated cognitive outcome(s) | Representative evidence | Practical message |
|---|---|---|---|
| BP | All-cause dementia; Alzheimer's disease; broader neurologic comorbidity | Systematic review/meta-analysis and multiple cohort/case-control studies support an association; BP180-related autoimmunity provides biologic plausibility. | Use cognitive screening and delirium-risk review before systemic corticosteroids; align steroid-sparing strategy, topical feasibility, itching control, infection prevention, and caregiver training. |
| HZ | Incident dementia; vascular cognitive impairment; higher concern after CNS involvement | Population-based cohorts link HZ with subsequent dementia, while antiviral therapy and zoster vaccination are associated with lower risk. | Treat HZ as a sentinel neurocutaneous event when ophthalmic, CNS-involved, or severe; prioritize vaccination, prompt antivirals, pain/sleep control, and follow-up for delirium or executive decline. |
| Psoriasis | All-cause dementia; Alzheimer's disease; possible cognitive impairment | Systematic reviews/meta-analyses suggest a modest excess risk, although some studies are heterogeneous or null. | Treat psoriasis as a systemic inflammatory disease and address cardiovascular, mood, and lifestyle comorbidities. |
| AD | All-cause dementia; neurocognitive burden related to sleep loss, itching, and inflammation | Recent meta-analysis suggests a modest association, but causal inference remains uncertain; symptom burden is substantial. | Use nocturnal itching and fragmented sleep as cognitive biomarkers; track caregiver-reported sleep, simplify topical regimens, and treat inflammation early. |
| Rosacea | All-cause dementia; Alzheimer's disease | A nationwide Danish cohort found increased risk of dementia and especially Alzheimer's disease; a 2024 commentary highlighted rosacea as an underappreciated dementia-associated dermatosis. | Ask older patients with persistent inflammatory rosacea about memory symptoms, sleep, and medication burden; treat rosacea as a chronic inflammatory disorder rather than a cosmetic condition. |
| PN/chronic prurigo | Measured cognitive impairment; severe daytime dysfunction; sleep-related cognitive burden | Inpatient data documented cognitive impairment in PN, and phase 2/3 studies confirm profound itching and sleep disturbance as treatable disease domains. | Quantify nocturnal scratching and sleep disruption with diaries or actigraphy when possible; use targeted itching control as a brain-relevant intervention. |
| Chronic pruritus/xerosis in older adults | Sleep disruption, inattention, low mood, daytime dysfunction; may worsen apparent cognition | High symptom burden and reduced quality of life are consistently documented, especially in older adults. | Perform medication reconciliation, xerosis repair, itching control, and sleep-risk review before escalating sedating or anticholinergic drugs. |

*Abbreviations*: BP, bullous pemphigoid; HZ, herpes zoster; CNS, central nervous system; AD, atopic dermatitis; PN, prurigo nodularis.

of dementia in older adults (*19-21*). These findings do not indicate that recombinant zoster vaccine is a dementia treatment, but they do reinforce the broader principle that prevention of dermatological disease may have neurological relevance. Current immunization recommendations already support 2-dose recombinant zoster vaccination in adults age ≥ 50 years and in immunocompromised adults age ≥ 19 years (*22,23*).

The mechanistic bridge is also stronger in HZ than in most inflammatory dermatoses because VZV is neurotropic, infects vascular endothelium, and activates inflammasome and amyloid-related pathways. Clinically, complicated HZ should therefore be considered a sentinel neurocutaneous event rather than an isolated rash, and particularly in older adults with delirium, gait decline, or new executive dysfunction.

The association between psoriasis and dementia appears more modest and heterogeneous, and yet the direction of the evidence is generally consistent with a systemic inflammatory link. Systematic reviews and meta-analyses suggest a small excess dementia risk in psoriasis, supported by a nationwide cohort study showing increased risk of Alzheimer's disease (*24-26*). Likewise, a recent meta-analysis found that AD was associated with all-cause dementia in longitudinal cohorts, although Mendelian randomization did not confirm a clear causal genetic effect (*27*). Importantly, both psoriasis and AD are now regarded as multisystem inflammatory diseases with important comorbidity implications, and both can produce chronic pruritus, fatigue, poor sleep, anxiety, depression, and reduced physical activity—factors that may worsen cognition even before formal dementia is diagnosed (*28-37*).

The dermatological spectrum is probably broader than these four entities. In a Danish nationwide cohort, rosacea was associated with increased dementia and especially Alzheimer's disease risk, with higher estimates in patients diagnosed in specialist settings (*38,39*). Prurigo nodularis also deserves attention: measurable cognitive impairment has been documented in inpatients, and the disorder couples intense IL-31-induced itching to repeated nocturnal arousal, anxiety, and compulsive

scratching (*40-42*). Even when frank dementia is absent, these states can worsen executive function, medication adherence, and day–night behavioral stability in older adults.

## 4. How a skin-brain inflammatory axis may operate

### 4.1. Neuroinflammation

The first axis places chronic cutaneous inflammation in direct conversation with the aging brain. Psoriasis, AD, BP, rosacea, and chronic prurigo can export IL-1β, IL-6, TNF-α, IL-17A/F, IL-23, IL-4, IL-13, IL-31, TSLP, and IL-33 into systemic circulation, where endothelial activation and blood-brain barrier (BBB) vulnerability can amplify microglial and astrocytic responses (*10,28,30,34,43*). BP adds a disease-specific autoimmune trigger: neuronal isoforms of BP180/collagen XVII and BP230/dystonin make epitope spreading a plausible route by which neurodegeneration and cutaneous autoimmunity reinforce each other. This neuroinflammatory axis therefore integrates the former cytokine, BBB, microglial, barrier, dysbiosis, and BP autoantigen mechanisms into one measurable pathway (Table 2, Figure 1). Among the three axes, this is the strongest and most biologically coherent pathway: associations noted at the cohort level provide moderate epidemiologic support, the inflammation-BBB-neuroinflammation sequence is broadly accepted, and data emerging from an atopic dermatitis model implicate IL-17 in BBB disruption, neuroinflammation, and cognitive dysfunction (*28,30*). Nevertheless, these lines of evidence should not be read as direct proof that skin inflammation causes dementia.

### 4.2. Neurovascular injury

The second axis emphasizes vascular injury, with HZ/VZV reactivation as the clearest dermatological trigger. VZV can infect neural and vascular tissue, activate IL-6 production through TLR2-dependent NF-κB signaling, trigger NLRP3 inflammasome assembly with IL-1β processing, and create amyloidogenic cellular and plasma environments (*44-47*). Clinically, ophthalmic or CNS-involved zoster can converge on endothelial inflammation, vasculitis, thrombosis, white-matter ischemic injury, delirium, gait decline, and vascular cognitive impairment. Psoriasis and rosacea may contribute to the same axis through chronic endothelial activation and microvascular dysfunction, but HZ supplies the most specific and preventable neurovascular model (*17-21,24-28,38,39*). Compared to axis 1, this pathway is supported by strong general evidence that peripheral inflammation can degrade BBB integrity, but direct evidence that cutaneous disease itself causes neurovascular cognitive injury remains limited. The genetic or pathway overlap between psoriasis, AD, Alzheimer's disease, and Parkinson's disease is suggestive rather than definitive, and the vascular-inflammation model is biologically plausible but still largely inferential. For HZ/VZV, the zoster-brain vasculopathy-cognition chain is clinically important

**Table 2. Three-axis mechanisms linking skin disease and cognitive impairment**

| Mechanism | Dermatological examples | Molecular / clinical detail | Potential brain-level consequence | Interpretation |
|---|---|---|---|---|
| Axis 1: Neuroinflammation | Psoriasis, AD, BP, rosacea, PN/chronic prurigo | Cutaneous IL-1β, IL-6, TNF-α, IL-17/23, IL-4/13, IL-31, TSLP, and IL-33 can prime endothelium and BBB vulnerability; BP180/BP230 epitope spreading adds a disease-specific autoimmune bridge. | BBB dysfunction, microglial and astrocytic priming, cytokine amplification, reduced cognitive reserve | Unifies cytokines, BBB, microglia, barrier failure, dysbiosis, and BP autoantigen sharing into one testable pathway (Evidence level: strongest but still indirect). |
| Axis 2: Neurovascular injury | HZ/VZV reactivation; psoriasis and rosacea endothelial activation | VZV neurotropism, endothelial infection, vasculitis, thrombosis, ischemia, TLR2/NF-κB signaling, NLRP3 inflammasome activation, and amyloidogenic stress. | Vascular cognitive impairment, white-matter injury, delirium, gait decline, dementia acceleration | Most specific preventable bridge; supports vaccination, urgent antivirals, and neurovascular follow-up after complicated HZ (Evidence level: moderate/inferential; direct evidence limited). |
| Axis 3: Neurofunctional disruption | AD, PN, BP, chronic pruritus/xerosis | IL-31/TSLP sensory circuits, nocturnal itching, scratching, pain, fragmented sleep, sedating or anticholinergic drugs, systemic corticosteroids, infection, and frailty. | Attention and memory fluctuation, sleep-related cognitive burden, delirium vulnerability, functional decline | Most dermatology-specific clinical axis; nocturnal itching and actigraphy can become cognitive-risk indicators (Evidence level: clinically strong but indirect functional pathway). |

*Abbreviations*: BP, bullous pemphigoid; HZ, herpes zoster; CNS, central nervous system; AD, atopic dermatitis; PN, prurigo nodularis; VZV, varicella-zoster virus.

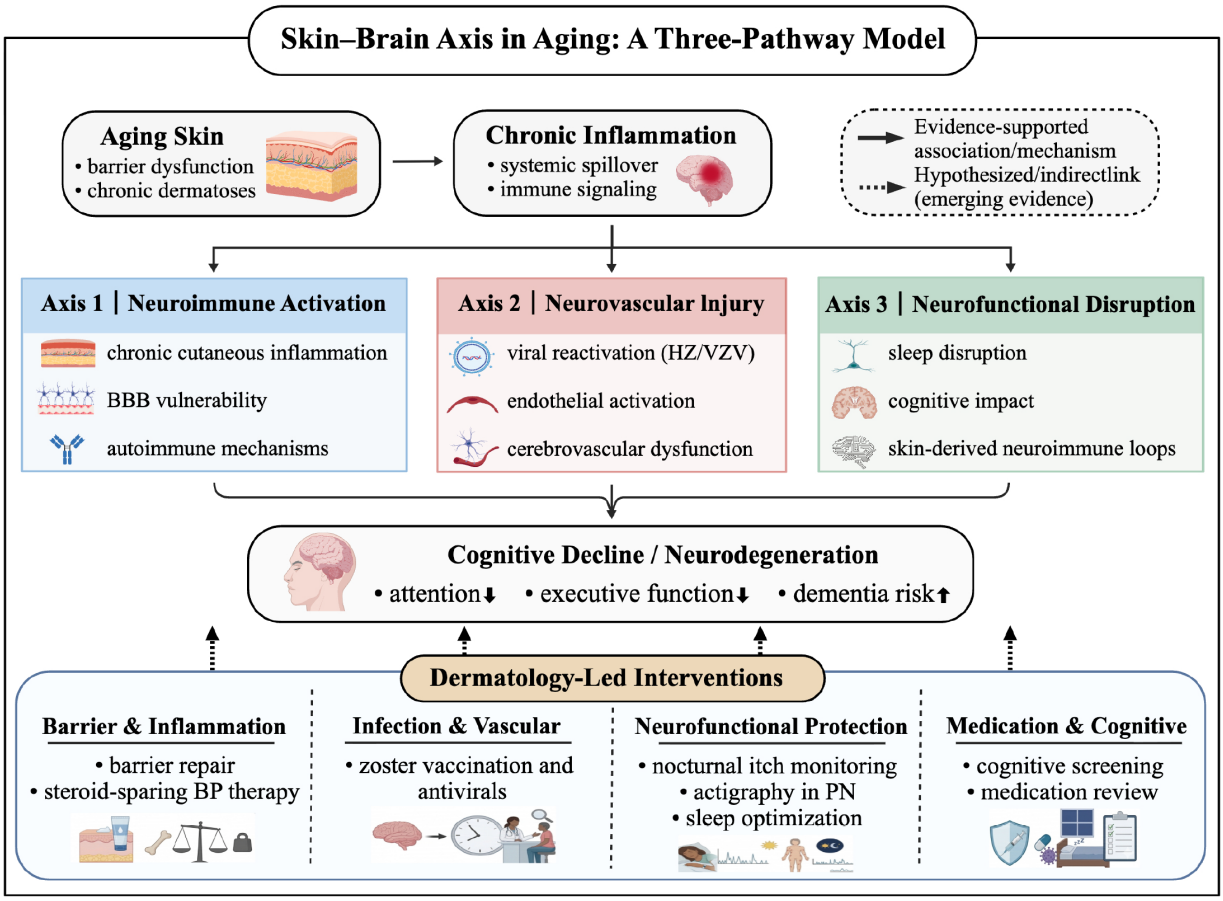


**Figure 1. Three-axis skin-brain framework for dermatological control as a dementia-modifying strategy.** Aging skin can function as a sentinel organ for neurodegeneration through Axis 1, neuroinflammation (cytokines, BBB vulnerability, microglia, and BP180/BP230-related autoimmunity); Axis 2, neurovascular injury (VZV, endothelial activation, vasculopathy, thrombosis, ischemia, and amyloidogenic stress); and Axis 3, neurofunctional disruption (itching, pain, fragmented sleep, medication toxicity, frailty, and delirium). Dermatology-led interventions--barrier repair, steroid-sparing BP therapy, cognitive screening before corticosteroids, zoster vaccination and antivirals, monitoring of nocturnal itching in AD, actigraphy in PN, sleep optimization, and a medication review--represent practical points at which clinicians can interrupt the pathway. Converging evidence suggests that these axes link cutaneous disease to brain vulnerability, although causality remains to be established. *Abbreviations*: BP, bullous pemphigoid; HZ, herpes zoster; PN, prurigo nodularis; BBB, blood-brain barrier; VZV, varicella-zoster virus.

but remains based on a handful of clinical observations rather than systematic causal evidence.

### 4.3. Neurofunctional disruption

The third axis depicts how skin disease degrades brain function even when structural neurodegeneration in not yet evident. Nocturnal itching, pain, burning, dysesthesia, scratching, and anxiety repeatedly fragment sleep, reduce slow-wave sleep, impair daytime attention, and disrupt circadian and autonomic stress responses. In AD and PN, IL-31-, TSLP-, periostin-, and IL-33-linked sensory-neuroimmune loops make itching both a symptom and a quantifiable brain-related mediator. In BP and chronic pruritus, sedating antihistamines, anticholinergics, opioids, systemic corticosteroids, infection, and frailty can compound chronic vulnerability with reversible confusion (*15,34,35,48*). This axis is especially dermatology-specific because itching intensity, nocturnal scratching, topical feasibility, actigraphy, and sleep response are directly visible and modifiable in skin clinics. The clinical evidence is convincing but mechanistically indirect: skin disease can reliably induce itching, pain, and sleep fragmentation, and sleep disturbance is a well-established contributor to cognitive decline, whereas evidence that this pathway directly causes structural neurodegeneration remains limited. Accordingly, axis 3 is best defined as a functional and behavioral route to cognitive vulnerability rather than a direct neurodegeneration mechanism.

## 5. Emerging interventional evidence: From dermatology trials to brain-related endpoints

A clearer evidence hierarchy helps preserve scientific caution without weakening the central message (Table 3). The strongest dementia-related signals currently come from zoster vaccine natural experiments and matched cohort analyses, followed by disease-specific epidemiology with biological specificity, mechanistic

**Table 3. Evidence hierarchy for dermatological control as a dementia-modifying strategy**

| Evidence tier | Evidence type | Representative examples | Brain-relevant inference | Dermatology-specific action |
|---|---|---|---|---|
| 1 | Quasi-experimental prevention signal | Live, recombinant, and AS01-adjuvanted zoster vaccine analyses | A visible skin-preventive intervention may alter dementia timing or diagnosis-free survival. | Make zoster vaccination review routine in dermatology and geriatric skin visits. |
| 2 | Disease-specific epidemiology plus biological specificity | BP with dementia and BP180/BP230 neurocutaneous autoimmunity; complicated HZ with cognitive outcomes | Certain dermatoses behave as sentinel organs for brain vulnerability rather than nonspecific comorbidities. | Use BP and complicated HZ as triggers for cognitive screening, delirium-risk review, and caregiver planning. |
| 3 | Mechanistic and experimental support | Cytokine-BBB-microglia signaling; VZV inflammasome and amyloidogenic signaling; endothelial activation | The three axes are biologically testable with inflammatory, vascular, imaging, sleep, and neurocognitive endpoints (The relative confidence differs by axis: Axis 1 is the strongest mechanistic pathway, Axis 2 is plausible but more speculative, and Axis 3 is clinically robust but functionally indirect). | Embed mechanistic sampling and cognitive outcomes into dermatology cohorts and trials. |
| 4 | Dermatology RCTs targeting brain-relevant mediators | BLISTER in BP; dupilumab in AD and PN; nemolizumab in PN; vascular imaging trials in psoriasis | Treatments already modify steroid burden, itching, sleep, scratching, or vascular inflammation--the mediators most likely to affect cognition. | Choose therapies with attention to sleep, itching, delirium, medication toxicity, and frailty rather than skin scores alone. |
| 5 | Clinic-level sentinel monitoring | Nocturnal itching in AD, actigraphy in PN, steroid decisions in BP, ocular/CNS HZ follow-up | Dermatology can identify risk earlier than memory clinics because the relevant signals are visible, symptomatic, and longitudinal. | Track nocturnal itching, scratching, topical feasibility, caregiver capacity, and medication burden as cognitive-risk indicators. |

*Abbreviations*: BP, bullous pemphigoid; HZ, herpes zoster; CNS, central nervous system; AD, atopic dermatitis; PN, prurigo nodularis; BBB, blood-brain barrier; VZV, varicella-zoster virus; RCTs, randomized controlled trials.

studies, and dermatology trials that improve brain-related mediators such as itching, sleep, steroid burden, and vascular inflammation. This ladder supports a practical translation: dermatological control should be evaluated not only by with skin clearance but also with delirium, sleep, cognitive fluctuations, gait, caregiver burden, medication toxicity, and biomarker endpoints. With regard to BP, the BLISTER trial showed that doxycycline was safer than prednisolone over 52 weeks as an initial strategy, a clinically meaningful finding for frail older adults at risk of delirium, infection, and steroid myopathy (*48*). With regard to AD, dupilumab produced rapid and sustained improvement in sleep across five randomized trials (*49*). With regard toa1 PN, dupilumab and nemolizumab alleviated itching and improved sleep within days to weeks (*41,42*). Psoriasis provides a useful cautionary note: vascular imaging endpoints in biologic trials have been more difficult to shift than cutaneous scores, indicating that brain-related pathways may need to be observed longer or measured using more specific biomarkers (*50*) (Table 4).

**6. What should clinicians do now?**

The key message is practical rather than speculative. Older adults and cognitively impaired patients should receive better care to prevent skin disease and be treated earlier, not only because skin disorders are distressing, but because uncontrolled cutaneous inflammation may contribute to broader neurologic vulnerability. For BP, guideline-concordant anti-inflammatory treatment, itching control, infection prevention, wound care, and steroid stewardship are essential (*15*). For HZ, vaccination, prompt antiviral treatment, and a closer neurological follow-up after a complicated infection are reasonable low-regret measures (*17-23*). For psoriasis and AD, clinicians should actively suppress inflammation, restore the barrier, address sleep and mood, simplify regimens, and avoid chronic systemic corticosteroids where modern guideline-supported options exist (*27,31-34,49*). These actions are summarized in Table 5.

For rosacea and chronic prurigo, clinicians should also think beyond appearance scores. Refractory burning, flushing, facial dysesthesia, or nocturnal pruritus may signal broader neurovascular or neuroimmune dysregulation, warranting explicit assessment of sleep quality, mood, subjective cognitive change, and caregiver burden. Across all older patients, medication reconciliation should specifically flag first-generation antihistamines, benzodiazepines, anticholinergic co-prescriptions, and repeated corticosteroid bursts.

**Table 4. Interventional and experimental evidence relevant to the skin-brain axis**

| Intervention/ condition | Design/population | Brain-relevant endpoint | Main results | Interpretation |
|---|---|---|---|---|
| Live zoster vaccine | Natural experiment in Wales; older adults eligible by birth-date cutoff | Incident dementia over 7 years | Vaccination associated with 20% relative reduction in new dementia diagnoses. | Best current quasi-experimental evidence that a dermatological preventive intervention may alter dementia risk (*20*). |
| Recombinant zoster vaccine (Shingrix) | Matched EHR-based natural experiment comparing recombinant *vs.* live vaccine | Time lived without dementia diagnosis | Recombinant vaccine associated with 17% longer diagnosis-free time, equivalent to 164 additional days without dementia diagnosis. | Supports a clinically meaningful vaccine signal and motivates trials focused on mechanism and causality (*19*). |
| Doxycycline-first strategy in BP | Pragmatic non-inferiority RCT; 253 analyzable BP patients, mean age 77.7 years | Severe/life-threatening/ fatal treatment-related events at 52 weeks | Short-term blister control was lower than prednisolone, but long-term severe adverse events were much lower with doxycycline (18.2% *vs* 36.3%). | Not a dementia trial, but highly relevant because steroid toxicity and frailty can worsen cognition in older BP patients (*48*). |
| Dupilumab in AD | Five randomized, double-blind, placebo-controlled trials, pooled N=2,632 | Sleep loss and sleep disturbance | Sleep improved rapidly and durably, with significant separation from placebo beginning in week 1-2. | Provides interventional support for the itching-sleep-cognition pathway (*49*). |
| Dupilumab in PN | Two randomized phase 3 trials (PRIME/PRIME2) | Worst itching NRS and skin lesion response | Both trials met primary and key secondary endpoints, with a marked reduction in itching and alleviation of lesions. | Demonstrates that one of the most cognitively burdensome itching disorders is now targetable with modern therapy (*41*). |
| Nemolizumab in PN | Phase 2 randomized trial/ post hoc sleep analysis | Sleep disturbance and scratching during sleep | Improvement in sleep disturbance emerged within days; actigraphy showed reduced scratching during sleep. | Particularly relevant to cognitive vulnerability induced by chronic nocturnal arousal (*42*). |
| Secukinumab in psoriasis (VIP-S) | Randomized placebo-controlled trial, $n = 91$ | Aortic vascular inflammation by FDG-PET/CT | Cutaneous improvement was achieved, but short-term vascular imaging improvement was neutral. | Important negative/neutral comparator showing that brain-relevant systemic endpoints may not normalize as quickly as skin scores (*50*). |

*Abbreviations*: BP, bullous pemphigoid; AD, atopic dermatitis; PN, prurigo nodularis.

Being mindful of the converse view is important. Patients with mild cognitive impairment or dementia are less able to report itching, adhere to topical regimens, recognize secondary infection, or tolerate burdensome full-body treatment plans. Dermatologists should therefore ask about memory impairment, missed medications, falls, nighttime agitation, and caregiver capacity when evaluating older patients with severe inflammatory dermatoses. Geriatricians and neurologists should add a routine skin inspection, xerosis care, itching screening, and a vaccination review to dementia care. A skin-limited model of care is no longer adequate for this population.

A practical research-ready workflow would include: baseline cognitive screening in older patients with BP, HZ, severe AD, severe psoriasis, rosacea with a substantial inflammatory burden, or chronic prurigo; structured recording of nocturnal itching and sleep loss; and longitudinal tracking of steroid exposure, vaccination status, falls, delirium, and caregiver-reported functional changes. These measures are simple enough for clinical use and could rapidly generate pragmatic data.

## 7. Conclusion

Healthy skin and healthy cognition should not be siloed. Current evidence does not prove that treating skin disease will prevent dementia, but it does support a biologically coherent and clinically actionable hypothesis: chronic skin inflammation, barrier dysfunction, viral reactivation, and itching-related physiological stress may all feed a skin-brain inflammatory axis. Accordingly, older adults and people with cognitive impairment should receive more proactive dermatological care, while older patients with severe skin disease need to be closely monitored for cognitive decline. An integrated approach is already justified on clinical grounds, and future prospective studies should determine how well it can protect the brain. The next generation of studies should pair dermatological interventions with brain-related endpoints—cognitive trajectory, delirium, actigraphy, endothelial biomarkers, neurofilament light, MRI white-matter burden, and pragmatic vaccination or steroid-sparing trials in older adults. Writings on this topic are most persuasive when they are honest about causality

**Table 5. Guideline-informed clinical actions at the skin-brain interface**

| Condition/ setting | Skin-focused action | Cognition-focused action | Guideline/consensus anchor | Key caveat |
|---|---|---|---|---|
| BP | Use guideline-concordant anti-inflammatory treatment, wound care, infection prevention, itching control, and steroid-sparing strategies; make cognitive status part of the treatment choice before systemic corticosteroids. | Document baseline cognition, delirium risk, falls, sleep disruption, caregiver ability to apply topical therapy, and steroid toxicity risk before starting systemic treatment. | EADV BP guideline | The key dermatology decision is not only which drug controls blisters, but which regimen is least likely to destabilize cognition in a frail patient. |
| HZ prevention in older adults | Administer 2-dose recombinant zoster vaccine to eligible adults; review vaccination status routinely. | Integrate vaccine review into memory-clinic, geriatric, and dermatology visits. | ACIP/CDC recommendations | Vaccination is not yet a proven dementia-prevention therapy despite encouraging observational data. |
| Acute HZ | Promptly start antivirals and monitor for ocular or CNS complications. | Watch for delirium, pain-related insomnia, and functional decline after infection. | Population-based cohort evidence plus standard HZ care principles | Neurologic risk appears highest with complicated or CNS-involved disease. |
| Psoriasis | Suppress systemic inflammation and optimize long-term disease control; assess metabolic and vascular comorbidities. | Screen for depression, sleep problems, vascular risk, and subjective cognitive complaints. | AAD-NPF psoriasis comorbidity guideline | The dementia signal is modest and heterogeneous; avoid overstating causality. |
| AD | Prioritize moisturization, barrier repair, topical anti-inflammatory therapy, and modern systemic options when indicated; avoid chronic systemic corticosteroids. | Treat nocturnal itching as a cognitive biomarker: track sleep diaries, caregiver reports, nighttime scratching, daytime attention, and regimen complexity. | AAD adult AD guidelines | Cognitive benefit is not yet proven, but itching and sleep are measurable, treatment-responsive mediators that dermatologists can monitor. |
| Rosacea | Treat by phenotype, suppress papulopustular inflammation, and control flushing/ocular disease using guideline-based therapy. | Ask about subjective cognitive change, migraine-like symptoms, sleep quality, and medication burden in older adults with persistent inflammatory disease. | S2K rosacea guideline | Direct intervention data on cognition are absent; action is currently based on epidemiologic and mechanistic plausibility. |
| PN/chronic prurigo | Use stepwise chronic-prurigo management and consider modern targeted therapy when disease is severe or sleep-disruptive; quantify scratching burden when possible. | Track nocturnal itching, concentration, mood, caregiver-reported day-night function, and actigraphy-derived scratching/sleep metrics when feasible. | PN guideline/expert guidance | Actigraphy can turn a skin symptom into a cognitive-risk signal and a trial endpoint, but implementation standards are still emerging. |
| Cross-cutting older adult/ dementia care | Perform a routine skin inspection, xerosis care, itching screening, wound surveillance, and medication reconciliation. | Classify patients by the three axes--neuroinflammation, neurovascular injury, and neurofunctional disruption--and flag first-generation antihistamines, benzodiazepines, anticholinergics, opioids, and repeated steroid bursts. | WHO dementia risk-reduction guidance and geriatric best practice | Only dermatology routinely observes the visible triggers--barrier failure, blistering, zoster, itching behavior, scratch injury, and topical feasibility--that make this prevention pathway actionable. |

*Abbreviations*: BP, bullous pemphigoid; HZ, herpes zoster; CNS, central nervous system; AD, atopic dermatitis; PN, prurigo nodularis.

and yet forward-thinking enough to envision where the field should go next.

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## References

1. World Health Organization. Ageing and health. Geneva: World Health Organization. *https://www.who.int/news-room/fact-sheets/detail/ageing-and-health* (accessed May 2, 2026).
2. Cheng Y, Han Y, Wang L, Ma J, Karako K, Shi Y, Song P. Pathways to embed digital health technologies and their governance mechanisms in Long-Term Care Insurance Systems: A comparative review of Japan, South Korea,

and China. Biosci Trends. 2026.
3. World Health Organization. Dementia. Geneva: World Health Organization. *https://www.who.int/news-room/fact-sheets/detail/dementia* (accessed May 2, 2026).
4. Nichols E, Steinmetz JD, Vollset SE, *et al*. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019. Lancet Public Health. 2022; 7:e105-e125.
5. Yao D, Gong X, Ma Y, Gong T, Wang G. The prevalence and interventions of xerosis cutis among older adults: A systematic review and meta-analysis. Geriatr Nurs. 2023; 54:219-228.
6. Kottner J, Fastner A, Lintzeri D-A, Blume-Peytavi U, Griffiths CEM, LeBlanc K. Skin health of community-living older people: A scoping review. Arch Dermatol Res. 2024; 316:374.
7. Sefcik JS, McLaurin EJ, Bass EJ, DiMaria-Ghalili RA. Chronic wounds in persons living with dementia: An integrative review. Int J Older People Nurs. 2022; 17:e12447.
8. Livingston G, Huntley J, Liu KY, *et al*. Dementia prevention, intervention, and care: 2024 report of the Lancet Standing Commission. Lancet. 2024; 404:572-628.
9. Chowdhary N, Barbui C, Anstey KJ, *et al*. Reducing the risk of cognitive decline and dementia: WHO recommendations. Front Neurol. 2022; 12:765584.
10. Kim HS, Jung H, Park YH, Heo SH, Kim S, Moon M. Skin-brain axis in Alzheimer's disease - Pathologic, diagnostic, and therapeutic implications: A hypothetical review. Aging Dis. 2024; 16:901-916.
11. Zhou Q, Xiong Z, Yang D, Xiong C, Li X. The association between bullous pemphigoid and cognitive outcomes in middle-aged and older adults: A systematic review and meta-analysis. PLoS One. 2023; 18:e0295135.
12. Phuan CZY, Yew YW, Tey HL. Bullous pemphigoid and antecedent neurological diseases: An association with dementia. Indian J Dermatol Venereol Leprol. 2017; 83:457-461.
13. Kokkonen N, Herukka SK, Huilaja L, Kokki M, Koivisto AM, Hartikainen P, Remes AM, Tasanen K. Increased levels of the bullous pemphigoid BP180 autoantibody are associated with more severe dementia in Alzheimer's disease. J Invest Dermatol. 2017; 137:71-76.
14. Tuusa J, Lindgren O, Tertsunen HM, Nishie W, Kokkonen N, Huilaja L, Izumi K, Herukka SK, Miettunen J, Shimizu H, Remes AM, Tasanen K. BP180 autoantibodies target different epitopes in multiple sclerosis or Alzheimer's disease than in bullous pemphigoid. J Invest Dermatol. 2019; 139:293-299.
15. Borradori L, Van Beek N, Feliciani C, *et al*. Updated S2K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol. 2022; 36:1689-1704.
16. Lu L, Chen L, Xu Y, Liu A. Global incidence and prevalence of bullous pemphigoid: A systematic review and meta-analysis. J Cosmet Dermatol. 2022; 21:4818-4835.
17. Bae S, Yun SC, Kim MC, Yoon W, Lim JS, Lee SO, Choi SH, Kim YS, Woo JH, Kim SY, Kim SH. Association of herpes zoster with dementia and effect of antiviral therapy on dementia: A population-based cohort study. Eur Arch Psychiatry Clin Neurosci. 2021; 271:987-997.
18. Schmidt SAJ, Veres K, Sorensen HT, Obel N, Henderson VW. Incident herpes zoster and risk of dementia: A population-based Danish cohort study. Neurology. 2022; 99:e660-e668.
19. Taquet M, Dercon Q, Todd JA, Harrison PJ. The recombinant shingles vaccine is associated with lower risk of dementia. Nat Med. 2024; 30:2777-2781.
20. Eyting M, Xie M, Michalik F, *et al*. A natural experiment on the effect of herpes zoster vaccination on dementia. Nature. 2025; 641:438-446.
21. Rayens E, Sy LS, Qian L, Ackerson BK, Tubert J, Luo Y, Modha PP, Calderon RO, Chmielewski-Yee E, Oraichi D, Yun H, Koro C, Tseng HF. Recombinant zoster vaccine is associated with a reduced risk of dementia. Nat Commun. 2026; 17:2056.
22. Anderson TC, Masters NB, Guo A, Shepersky L, Leidner AJ, Lee GM, Kotton CN, Dooling KL. Use of recombinant zoster vaccine in immunocompromised adults aged ≥ 19 years: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022; 71:80-84.
23. Ma YN, Karako K, Song P, Xia Y. Can the herpes zoster vaccination be a strategy against dementia? Drug Discov Ther. 2025; 19:124-128.
24. Zhao J, Li T, Wang J. Association between psoriasis and dementia: A systematic review. Neurologia (Engl Ed). 2024; 39:55-62.
25. Charoenngam N, Rittiphairoj T, Ponvilawan B, Ungprasert P. Patients with psoriasis have a higher risk of dementia: A systematic review and meta-analysis. Indian J Dermatol Venereol Leprol. 2021; 87:364-370.
26. Kim M, Park HE, Lee SH, Han K, Lee JH. Increased risk of Alzheimer's disease in patients with psoriasis: A nationwide population-based cohort study. Sci Rep. 2020; 10:6454.
27. Gwak YS, Kim SY, Woo CE, Shin K, Son E, Kim JW, Kim SJ, Song TJ, Park HR, Kim K, Ko DS, Kim YH. Association between atopic dermatitis and dementia: Evidence from systematic review, meta-analysis, and Mendelian randomization. Acta Derm Venereol. 2025; 105:adv41321.
28. Elmets CA, Leonardi CL, Davis DMR, *et al*. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol. 2019; 80:1073-1113.
29. Yang J, Zhang S, Wu Q, Chen P, Dai Y, Long J, Wu Y, Lin Y. T cell-mediated skin-brain axis: Bridging the gap between psoriasis and psychiatric comorbidities. J Autoimmun. 2024; 144:103176.
30. Cameron S, Donnelly A, Broderick C, Arichi T, Bartsch U, Dazzan P, Elberling J, Godfrey E, Gringras P, Heathcote LC, Joseph D, Wood TC, Pariante C, Rubia K, Flohr C. Mind and skin: Exploring the links between inflammation, sleep disturbance and neurocognitive function in patients with atopic dermatitis. Allergy. 2024; 79:26-36.
31. Davis DMR, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM, Eichenfield LF, Frazer-Green L, Paller AS, Silverberg JI, Singh AM, Sidbury R. American Academy of Dermatology guidelines: Awareness of comorbidities associated with atopic dermatitis in adults. J Am Acad Dermatol. 2022; 86:1335-1336.e18.
32. Davis DMR, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM, Eichenfield LF, Frazer-Green L, Paller AS, Schwarzenberger K, Silverberg JI, Singh AM, Wu PA, Sidbury R. Guidelines of care for the management

of atopic dermatitis in adults with topical therapies. J Am Acad Dermatol. 2023; 89:e1-e20.
33. Davis DMR, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM, Eichenfield LF, Frazer-Green L, Paller AS, Schwarzenberger K, Silverberg JI, Singh AM, Wu PA, Sidbury R. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. J Am Acad Dermatol. 2024; 90:e43-e56.
34. Butler DC, Berger T, Elmariah S, *et al*. Chronic pruritus: A review. JAMA. 2024; 331:2114-2124.
35. Bollemeijer JF, De Veer MR, Weisshaar E, Brouwer WP, Lahousse L, Gunn DA, Nijsten TEC, Pardo LM. Chronic pruritus in older adults: Prevalence, associations, and pruritus-specific quality of life. Acta Derm Venereol. 2025; 105:adv42396.
36. Benn CS, Netea MG, Selin LK, Aaby P. A small jab - A big effect: Nonspecific immunomodulation by vaccines. Trends Immunol. 2013; 34:431-439.
37. Waheed G, Ramadan G, Mohammed HA. Enzymatically-modified isoquercitrin alleviates skin inflammation, mast cell degranulation, and vascular hyperpermeability in a mouse model of plaque psoriasis. Int Immunopharmacol. 2026.
38. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Patients with rosacea have increased risk of dementia. Ann Neurol. 2016; 79:921-928.
39. Abdi P, Haq Z, Diaz MJ, Maibach HI, Ogunyemi B. Rosacea as a potential risk factor for dementia. Int J Dermatol. 2024; 63:e200-e202.
40. Lanza G, Cosentino FII, Ferri R, Lanuzza B, Siragusa M, Tripodi M, Schepis C. Cognitive impairment in inpatients with prurigo nodularis and psychiatric comorbidities. Int J Environ Res Public Health. 2021; 18:6265.
41. Yosipovitch G, Mollanazar N, Ständer S, *et al*. Dupilumab in patients with prurigo nodularis: Two randomized, double-blind, placebo-controlled phase 3 trials. Nat Med. 2023; 29:1180-1190.
42. Ständer S, Yosipovitch G, Lacour JP, Legat FJ, Paul C, Reich A, Chaouche K, Ahmad F, Piketty C. Nemolizumab efficacy in prurigo nodularis: Onset of action on itch and sleep disturbances. J Eur Acad Dermatol Venereol. 2022; 36:e943-e946.
43. Wilson SR, Thé L, Batia LM, *et al*. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. Cell. 2013; 155:285-295.
44. Wang JP, Kurt-Jones EA, Shin OS, Manchak MD, Levin MJ, Finberg RW. Varicella-zoster virus activates inflammatory cytokines in human monocytes and macrophages *via* Toll-like receptor 2. J Virol. 2005; 79:12658-12666.
45. Nour AM, Reichelt M, Ku CC, Ho MY, Heineman TC, Arvin AM. Varicella-zoster virus infection triggers formation of an interleukin-1β (IL-1β)-processing inflammasome complex. J Biol Chem. 2011; 286:17921-17933.
46. Bubak AN, Beseler C, Como CN, Tyring SK, Haley C, Mescher T, Hassell JE Jr, Cohrs RJ, Potter H, Nagel MA. Acute zoster plasma contains elevated amyloid, correlating with Aβ42 and amylin levels, and is amyloidogenic. J Neurovirol. 2020; 26:422-428.
47. Bubak AN, Como CN, Coughlan CM, Johnson NR, Hassell JE, Mescher T, Niemeyer CS, Mahalingam R, Cohrs RJ, Boyd TD, Potter H, Russ HA, Nagel MA. Varicella-zoster virus infection of primary human spinal astrocytes produces intracellular amylin, amyloid-β, and an amyloidogenic extracellular environment. J Infect Dis. 2020; 221:1088-1097.
48. Williams HC, Wojnarowska F, Kirtschig G, Mason J, Godec TR, Schmidt E, Chalmers JR, Childs M, Walton S, Harman K, Chapman A, Whitham D, Nunn AJ; UK Dermatology Clinical Trials Network BLISTER Study Group. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: A pragmatic, non-inferiority, randomised controlled trial. Lancet. 2017; 389:1630-1638.
49. Beck LA, Silverberg JI, Simpson EL, Yosipovitch G, Eckert L, Guillemin I, Chen Z, Ardeleanu M, Plaum S, Graham N, Ruddy M, Pirozzi G, Gadkari A. Dupilumab significantly improves sleep outcomes in adult patients with atopic dermatitis: Results from five randomized clinical trials. J Eur Acad Dermatol Venereol. 2021; 35:e130-e133.
50. Gelfand JM, Shin DB, Duffin KC, *et al*. A randomized placebo-controlled trial of secukinumab on aortic vascular inflammation in moderate-to-severe plaque psoriasis (VIP-S). J Invest Dermatol. 2020; 140:1784-1793.e2.

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