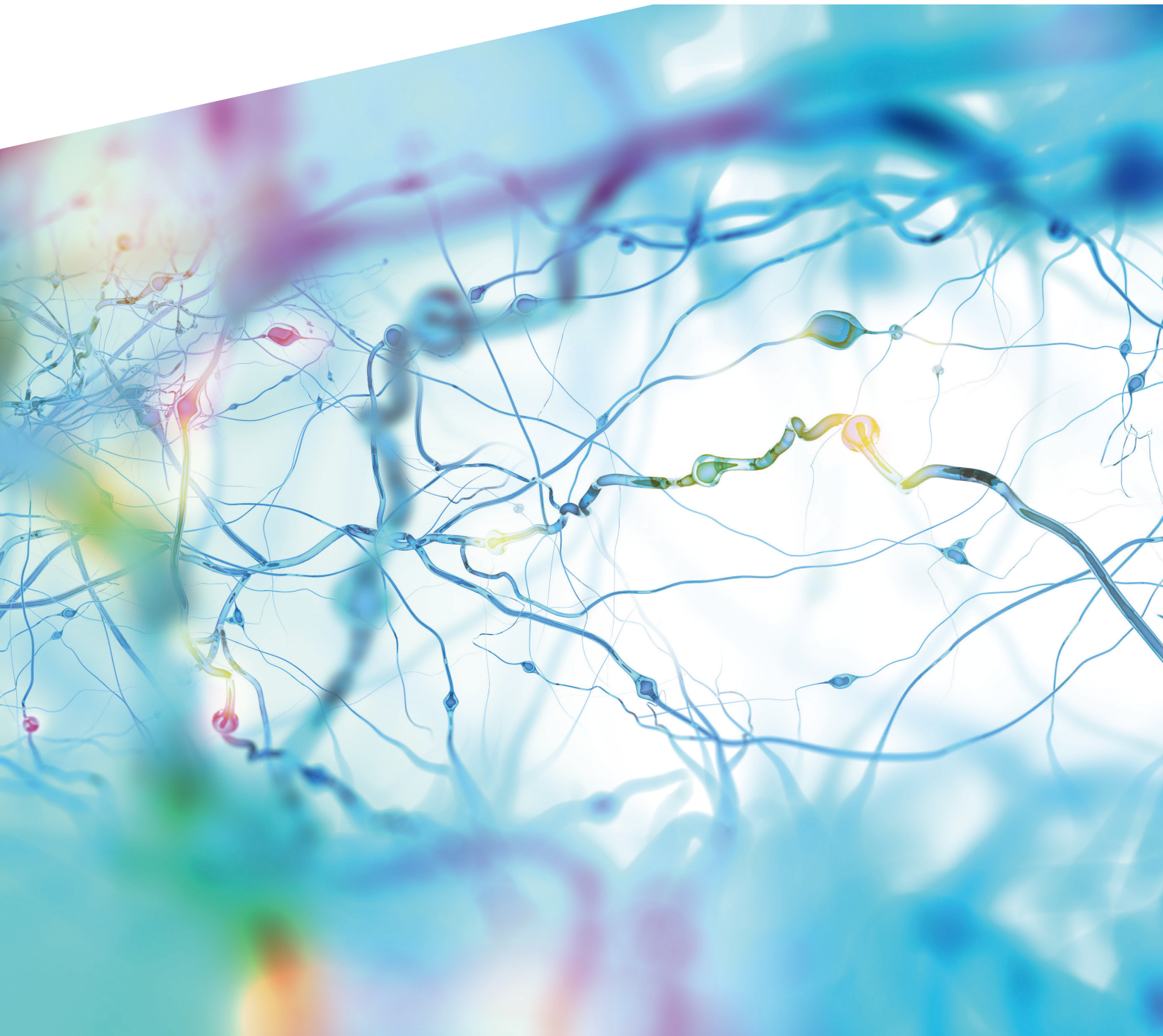
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Aims & scope

Aims

Ewha Medical Journal aims to provide medical professionals with essential healthcare information and fundamental medical knowledge. The journal will contribute to improving and serving human society based on the Christian values of education, truth, goodness, and beauty. Additionally, the journal strives to nurture young editors, enabling them to demonstrate exceptional women's editorial leadership and provide innovative learning methods.

Scope

Its scope includes:

- Up-to-date medical knowledge and skills essential for patient care
- Preparing for the future of medicine
- Effective interprofessional communication
- Ensuring gender equity and diversity
- Medical education materials
- Sharing data and protocols

Regional scope

The journal primarily focuses on Korea but welcomes submissions from researchers worldwide.

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Editorial

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The Ewha Medical Journal

In this issue: October 2026

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Medical progress depends not only on generating new knowledge, but also on interpreting evidence accurately, communicating it responsibly, and applying it to decisions appropriate for patients and populations. The eight articles in this issue address these tasks across dermatology, artificial intelligence (AI)-assisted scientific editing, epidemiology, pain medicine, diagnostic imaging, and genetic counseling education. They range from disease mechanisms and exposure recognition to population-level burden estimates, clinical decision-making, and experiential training.

"Irritant contact dermatitis: beyond a diagnosis of exclusion" presents irritant contact dermatitis as a distinct innate immune-mediated inflammatory disorder rather than merely a condition diagnosed after excluding allergic contact dermatitis. The review integrates current knowledge of barrier dysfunction, inflammatory pathways, host susceptibility, occupational exposure, diagnosis, treatment, and prevention.

"Korean Standard Series allergens and emerging sources" updates patient information on allergens included in the Korean Standard Series, which has not been revised for more than 2 decades. It addresses contemporary exposures involving electronic devices, personal protective equipment, nail products, and children's toy slime and provides Korean-language materials to support allergen avoidance and occupational counseling.

"Language editing in the artificial intelligence era: achieving epistemic integrity," provided as an expanded Korean translation, examines how AI-generated revisions may alter the certainty, scope, or interpretation of scientific claims. It emphasizes the continuing importance of human oversight in keeping the language of a manuscript aligned with the research evidence.

Two studies use Global Burden of Disease 2021 data to examine population health. "The burden of neck pain across US states, 1990–2021" identifies geographic, sex-, and age-related variation, with modest declines in age-standardized rates despite rising case counts. "Global, regional, and national burden of motor neuron diseases, 1990–2021" estimates that the absolute burden increased worldwide and that age-standardized mortality rose even as age-standardized prevalence and incidence declined slightly. Both provide estimates relevant to healthcare planning and resource allocation, and the neck pain study also points to age- and region-specific prevention.

A retrospective pilot study investigates whether the psoas-lumbar vertebral index, an imaging-based marker of central sarcopenia, predicts short-term pain relief after pulsed radiofrequency treatment for postherpetic neuralgia. No detectable association was found in the small cohort, while the exploratory sex difference warrants evaluation in larger prospective studies.

A case of spontaneous retrobulbar hematoma demonstrates how serial computed tomography and magnetic resonance imaging can distinguish a resolving hematoma from a hemorrhagic neoplasm. Progressive resolution supported conservative management and helped avoid an unnecessary invasive procedure.

Finally, "Role-play in graduate genetic counseling education" describes a 6-week practicum involving 22 simulated counseling scenarios. Completed without external clinical sites or supervisors, the program offers a feasible model for experiential education when clinical placements are limited.

This combination of current evidence, responsible communication, and practice-oriented learning reflects the journal's aim to support patient care while preparing readers for changing medical and educational environments.

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Authors' contribution

All work was completed by Ji Yeon Byun.

Conflict of interest

Ji Yeon Byun has served as the editor of the *Ewha Medical Journal* since January 2026. However, she was not involved in the peer review process or decision-making for this article. No other potential conflicts of interest relevant to this article were reported.

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Review article

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The Ewha Medical Journal

Irritant contact dermatitis: beyond a diagnosis of exclusion

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Irritant contact dermatitis (ICD) is the most common form of contact dermatitis and a leading cause of occupational skin disease, but remains underrecognized relative to allergic contact dermatitis (ACD). Direct chemical or physical injury to the epidermal barrier causes ICD, which can develop in anyone when exposure intensity or duration exceeds the skin's repair capacity. ICD is increasingly understood to involve more than barrier disruption: it is an innate immune-mediated inflammatory disorder involving keratinocyte-derived cytokines, neutrophil recruitment, C-C motif chemokine ligand 2–C-C motif chemokine receptor 2–interleukin-1β signaling, Toll-like receptor 3, and inflammasome activation. Host factors, particularly atopic dermatitis and filaggrin loss-of-function variants, further influence susceptibility. Clinical phenotypes range from acute irritant reactions to chronic cumulative dermatitis, and occupational wet work is a major preventable exposure. Distinguishing ICD from ACD is difficult because their clinical and histopathological features overlap, they may coexist, and ICD-related barrier damage may facilitate subsequent allergic sensitization. Diagnosis therefore requires assessment of exposure history, lesion distribution, symptom quality, and temporal course, with patch testing when ACD is suspected. Molecular biomarker panels and noninvasive imaging or barrier-assessment techniques may improve diagnostic precision, but remain investigational. Management should prioritize identifying and removing irritants, reducing exposure, implementing appropriate protective measures, and restoring the epidermal barrier. Recognizing ICD as a distinct clinical entity, rather than simply a diagnosis of exclusion, is essential for accurate diagnosis and effective management of contact dermatitis in clinical practice.

Keywords: Contact dermatitis; Irritant dermatitis; Occupational dermatitis

Introduction

Irritant contact dermatitis (ICD) is a nonspecific inflammatory skin reaction to direct chemical or physical damage to the epidermal barrier and is the most common form of contact dermatitis (CD). It accounts for approximately 80% of CD cases, representing a substantial clinical burden [1]. Its burden is particularly pronounced in occupational settings. Occupational CD accounts for most occupational skin diseases (OSD)—up to 95% in some reports—and irritant exposures or ICD constitute the predominant subtype, accounting for approximately 70%–80% of occupational CD or OSD in registry studies [2-4]. High-risk groups include healthcare workers, hairdressers and beauty workers, food handlers, construction workers, and people in other occupations involving wet work or chemical exposure [3].

Unlike allergic contact dermatitis (ACD), ICD requires no prior sensitization and can develop in virtually anyone after exposure to an irritant of sufficient concentration and duration. Despite this fundamental immunological distinction, ICD has long received less clinical and research attention than ACD. One reason is that the 2 conditions often cannot be distinguished reliably on clinical or histopathological grounds. They may coexist or develop sequentially in the same patient, and ICD often precedes and facilitates ACD. ICD should therefore be understood systematically as an independent clinical entity, rather than simply a diagnosis reached after excluding ACD.

This review begins with the definition and epidemiology of ICD, then examines its pathophysiological mechanisms and host risk factors. It also discusses clinical phenotypes, diagnosis, the relationship with ACD, occupational aspects and hand eczema, and current treatment and prevention approaches.

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Ethics statement

Because this study is based on the literature, institutional review board approval and informed consent were not required.

Pathophysiology

Barrier disruption and cytokine cascade

Disruption of the epidermal permeability barrier is central to ICD. After an irritant passes through the stratum corneum into the viable epidermis, damaged corneocytes and activated keratinocytes release proinflammatory mediators that initiate an inflammatory cascade [2]. Conceptually, the process has 3 sequential steps: skin barrier disruption, epidermal cell activation, and cytokine release that stimulates innate immunity, leading to inflammation and tissue damage [2]. Implicated cytokines and chemokines include interleukin (IL)-1α, IL-1β, tumor necrosis factor-α (TNF-α), IL-6, C-X-C motif chemokine ligand 8/IL-8, C-C motif chemokine ligand 2 (CCL2), C-C motif chemokine ligand 20, C-C motif chemokine ligand 21, and interferon γ [2,5]. These events explain the current understanding of ICD as an innate immune response to direct barrier and cellular injury.

Molecular pathways and innate immune activation

Recent studies have begun to clarify molecular pathways within this cytokine cascade. In surfactant-induced ICD, signaling through CCL2 and C-C motif chemokine receptor 2 (CCR2) in skin-resident cells drives IL-1β release and subsequent neutrophil recruitment to the injury site [5]. In a murine model of cumulative ICD induced by sodium lauryl sulfate (SLS; also called sodium dodecyl sulfate in some studies), CCL2 expression increased in SLS-treated skin. Both local CCL2 blockade and CCR2 deficiency reduced skin inflammation, epidermal thickening, and neutrophil accumulation [5]. Intradermal IL-1β restored neutrophil accumulation and ICD development in *CCR2*-deficient mice, further supporting a central role for the CCL2–CCR2–IL-1β axis in surfactant-induced ICD [5].

Molecular responses can begin soon after irritant exposure. Genome-wide expression analysis of human epidermis irritated in vivo by SLS or nonanoic acid (NON) identified distinct expression profiles within 30 minutes. NON transiently induced IL-6 and mitogen-activated protein kinase-related pathways, whereas SLS transiently downregulated pathways involved in cellular energy metabolism [6]. These results demonstrate early molecular responses in ICD pathogenesis and suggest that different irritants may produce distinct molecular signatures.

Innate immune receptor signaling also appears to contribute to ICD. Toll-like receptor 3 (TLR3) has been implicated in both ACD and ICD. In a croton oil-induced murine ICD model, *TLR3*-deficient mice had less inflammation, whereas *TLR3*-transgenic mice had more, suggesting that TLR3 amplifies antigen-independent cutaneous inflammation [7]. Inflammasome activation is another pathway of interest alongside Toll-like receptor signaling. Irritants can induce cell necrosis, cellular stress, and damage-associated molecular patterns, potentially activating the NLR family pyrin domain-containing 3 (NLRP3) inflammasome [8]. NLRP3 activation triggers caspase-1-dependent processing of pro-IL-1β and pro-IL-18, amplifying neutrophilic and innate inflammatory responses [8]. In a human patch-test model, topical inflammasome inhibition with disulfiram reduced SLS-induced irritation. This supports the relevance of inflammasomes to ICD and suggests that inflammasome-dependent IL-1 family cytokine signaling may be a therapeutic target [8].

Molecular distinction from allergic contact dermatitis

Molecular studies may help distinguish ICD from ACD: analyses of patch-test biopsies associate ICD with tissue remodeling and proliferative pathways, whereas ACD has a distinct immune activation signature [9,10]. A proposed small biomarker panel for distinguishing allergic from irritant reactions comprises *CD8A*, *CD4*, *GNLY*, *GZMB*, *CD69*, *IFNG*, *CXCL10*, *HLA-DRA*, *GPR183*, *PLEK*, *IL15*, and *IGFL3* [9,10]. Most allergy-associated biomarkers are not upregulated in ICD, consistent with the absence of allergen-specific T-cell activation [9]. In active dermatitis lesions, this approach showed substantial agreement with clinical diagnoses, supporting molecular profiling as a promising means of distinguishing ICD from ACD [10]. These tools remain investigational, however, and routine differentiation still requires patch testing with careful clinical correlation.

Host risk factors

The extent and outcome of barrier disruption differ substantially among individuals, reflecting variation in susceptibility to ICD [2,11]. Responsiveness also depends on the irritant, because different agents act through different mechanisms and elicit distinct molecular responses [2,6,11]. Greater susceptibility to one irritant therefore does not necessarily imply greater susceptibility to another [2,6,11]. Among personal risk factors, atopic dermatitis (AD) has the strongest supporting evidence: individuals with AD have a lower threshold for developing ICD and a poorer prognosis than nonatopic individuals [4,12]. This susceptibility is attributed to the intrinsic epidermal barrier defect in AD, which facilitates irritant penetration and amplifies inflammation. Consistent with this mechanism, a systematic review and meta-analysis of occupa-

tional CD risk factors found AD to be one of the most consistently supported personal risk factors, reinforcing the central role of barrier integrity in ICD pathophysiology [4].

Genetic factors have also been implicated: filaggrin loss-of-function mutations are associated with increased susceptibility to chronic ICD and chronic hand dermatitis, likely through impaired stratum corneum integrity and reduced barrier resilience [12]. Inflammatory responsiveness may also vary with *TNFA* polymorphisms. Greater susceptibility to hand ICD has been associated with *TNFA-308*, whereas *TNFA-238* appears relatively protective. These findings suggest that host cytokine response profiles may influence irritant reactivity [13].

Age, sex, and ethnicity may influence irritant responsiveness, although the evidence is inconsistent. Older adults may react less strongly despite impaired barrier repair, possibly because of reduced inflammation and cutaneous blood flow and smaller transepidermal water loss (TEWL) responses after irritant exposure in aged skin [2,11]. ICD and hand dermatitis are reported more often in women, but this is thought to reflect occupational and domestic exposure patterns, particularly greater wet-work exposure, rather than inherent biological susceptibility [11]. Some studies suggest stronger responses in Asian than in Caucasian skin; inconsistent findings, however, make ethnicity a possible modifier rather than a reliable predictor [14,15]. Overall, susceptibility to ICD depends on the combined effects of barrier integrity, inflammatory responsiveness, genetic background, anatomical site, demographic factors, and cumulative environmental exposure.

Clinical phenotypes and diagnosis

Clinical subtypes

ICD has diverse clinical phenotypes, reflecting interactions among the irritant, exposure concentration and mode, exposure duration and frequency, anatomical site, and individual endogenous factors [2,11,16]. It can follow either a single intense exposure or repeated low-level exposures that cumulatively exceed the skin's capacity to repair its barrier.

Table 1 summarizes the major ICD subtypes [17]. Chronic cumulative ICD is the most common and clinically important phenotype. It develops when repeated subthreshold exposures to weak irritants occur before the epidermal barrier has recovered fully from the previous exposure [16]. Typical features are xerosis, erythema, scaling, hyperkeratosis, and fissuring, usually without marked vesiculation [2,16]. Chronic cumulative ICD often overlaps clinically with ACD, contact urticaria, or AD, particularly in occupational hand dermatitis [16].

Anatomical site-specific manifestations

ICD can have characteristic presentations at specific anatomical sites because of regional differences in stratum corneum thickness, hydration, occlusion, friction, barrier recovery, and exposure patterns. Thin or frequently exposed skin, including the eyelids, face, genital area, and dorsal hands, is generally more susceptible to irritants. The palms and soles are relatively resistant because their stratum corneum is thicker [2]. Table 2 summarizes these site-specific manifestations [2,17].

Diagnosis

ICD is diagnosed primarily by integrating exposure history, lesion morphology, anatomical distribution, symptom quality, temporal course, and exclusion of relevant allergic sensitization [2,11,16]. Its traditional description as a diagnosis of exclusion should not imply a passive or residual diagnosis. Clinicians should actively suspect ICD when dermatitis begins where a plausible irritant contacts the skin, remains largely confined to that area, and correlates with exposure intensity, frequency, and duration [2,16].

Diagnosis requires a detailed history and physical examination focused on lesion distribution and morphology. Clinicians should assess occupational exposures, hobbies, domestic activities, environmental conditions, personal protective equipment (PPE), wet work, hand hygiene, glove use, cosmetics, topical and oral medications, and personal or family history of chronic skin disease [2,16]. Assessment should also cover the dose, frequency, and duration of exposure, the extent of exposed skin, and the cumulative exposure pattern [16]. A characteristic pattern in hand ICD is the apron pattern, in which interdigital dermatitis extends onto both palmar and dorsal surfaces [1]. Symptom timing is particularly informative: as noted above, ICD generally develops sooner after exposure than ACD [16]. Acute ICD usually peaks rapidly and then resolves in a decrescendo pattern, whereas ACD follows a delayed crescendo pattern over 24–96 hours after allergen exposure [1,16].

On examination, sharply defined lesions restricted to the directly exposed area favor ICD when burning, stinging, prickling, pain, or soreness predominate; predominant pruritus favors ACD [1,2,16]. ICD may also show accommodation, or the hardening phenomenon: skin reactivity gradually decreases and dermatitis resolves despite continued or repeated exposure to the same irritant. Experiments with repeated SLS exposure have shown that TEWL may peak after approximately 2 weeks and then improve during the third week despite ongoing exposure. This adaptive response may favor ICD over ACD [18].

Patch testing remains essential when ACD is suspected; when dermatitis is chronic, recurrent, occupational, or refractory to

Table 1. Clinical subtypes of irritant contact dermatitis

Subtype	Description	Typical irritants or triggers
Acute ICD	Rapid inflammation after a single intense exposure, clinically indistinguishable from ACD. Lesions are generally sharply demarcated and limited to the contact area; severity determines whether erythema, edema, vesiculation, bullae, erosions, or necrosis occurs.	Strong acids or alkalis, solvents, oxidizing agents, chemical spills, concentrated disinfectants
Delayed acute ICD/ subacute ICD	Develops several hours to 1–2 days after exposure. The delayed onset can mimic ACD, although the clinical presentation resembles acute ICD.	Anthralin, benzalkonium chloride, acrylates, benzoyl peroxide, nonanoic acid, certain topical medications
Chronic cumulative ICD	The most common form, arising from repeated subthreshold exposure to weak irritants before the barrier has fully recovered. Features include dryness, erythema, scaling, lichenification, hyperkeratosis, and fissuring, generally with less vesiculation than ACD.	Water, wet work, soaps, detergents, cleansers, shampoos, low-concentration disinfectants, repeated glove occlusion
Subjective/sensory irritation	Reproducible stinging, burning, prickling, pain, tightness, or itching within seconds to minutes, without visible lesions. May occur independently of susceptibility to other irritants.	Propylene glycol, hydroxy acids, lactic acid, tretinoin, ethanol-containing products, cosmetics
Non-erythematous/ suberythematous irritation	Early or subclinical barrier damage without visible erythema, detectable only by bioengineering methods such as TEWL, capacitance, or other barrier measurements.	Low-grade repeated exposure to surfactants, detergents, water, occlusion
Frictional ICD	Caused mainly by repeated mechanical friction or rubbing, often on the hands. May coexist with chemical irritation.	Repetitive manual work, paper handling, tools, textiles, gloves, rubbing from masks or devices
Traumatic ICD	Chronic ICD that uncommonly develops at a site of prior mechanical injury, abrasion, or laceration.	Repeated trauma, abrasions, wound care products, occupational microtrauma
Hyperkeratotic ICD	Well-demarcated hyperkeratotic plaques with minimal erythema and little vesiculation, occurring most often on the hands or feet. Biopsy may reveal chronic spongiotic dermatitis.	Chronic mechanical irritation, repeated wet work, detergents, occupational hand exposure
Asteatotic ICD	Dry, fissured, cracked eczema, usually in older adults or people with xerotic skin.	Low humidity, frequent washing, soaps, winter climate, decreased skin lipids
Acneiform/follicular ICD	Follicular papules or sterile pustules caused by irritant or occlusive exposure.	Metals, tars, asphalt, oils, greases, cutting fluids, cosmetics, occlusive topical products
Airborne ICD	Caused by airborne irritants and predominantly affects exposed areas. Particle deposition and runoff can also produce involvement of "shadowed" areas or skin folds.	Fiberglass, dusts, cement particles, sprays, volatile chemicals, aerosols

Adapted and revised from Ale and Maibach [17].
ICD, irritant contact dermatitis; ACD, allergic contact dermatitis; TEWL, transepidermal water loss.

treatment; or when patients are exposed to common allergens such as rubber accelerators, preservatives, fragrances, metals, hair dyes, topical medications, disinfectants, or cosmetics [1,4,16]. A negative result supports ICD only if the clinical history and exposure pattern are compatible. Such results require caution: in a North American Contact Dermatitis Group analysis, dermatitis was ultimately attributed to a relevant irritant in only 23% of patients with negative patch tests [19]. A negative test alone therefore does not establish ICD.

Noninvasive tools can assess barrier impairment, although most remain investigational. TEWL is widely used to measure barrier disruption, but variability due to external factors such as temperature and humidity limits its clinical utility [11,20]. It is therefore more useful in research or controlled occupational settings than in routine practice. Natural moisturizing factor (NMF) has been proposed as a more sensitive molecular marker of stratum corneum integrity. The dermal texture index, derived from corneocyte surface topography, has been investigated alongside NMF as a potential biomarker of irritant-induced barrier alterations [21,22]. Reflectance confocal microscopy (RCM) allows repeated, real-time observation of affected skin and can show stratum corneum disruption, parakeratosis, spongiosis, corneocyte separation, and inflammatory infiltrates [11,23]. These techniques nevertheless cannot yet replace careful clinical evaluation and patch testing.

Skin biopsy has limited diagnostic value because ICD, ACD, and other eczematous dermatoses can share patterns of spongiotic dermatitis [1,2,4]. Histopathological differentiation may help in early lesions, ideally within 24–48 hours of exposure [2]. Early ICD may show more pronounced epidermal necrosis, keratinocyte ballooning in the upper and middle epidermis, neutrophilic infiltration, and upper epidermal injury. ACD may instead show more pronounced lower-epidermal spongiosis, spongiotic vesicles, and persistent intraepidermal Langerhans cell infiltration [1]. Bains et al. [2] also noted that eosinophils favor ACD, neutrophils may support ICD, increased mast cells are more characteristic of AD, and granular layer changes can offer additional clues; none is

Table 2. Site-specific manifestations of irritant contact dermatitis

Anatomical site	Clinical features	Common irritants or predisposing factors
Hands	The most common site of occupational ICD, with dryness, erythema, scaling, fissuring, hyperkeratosis, and soreness. The dorsal hands and interdigital spaces are often more susceptible than the palms.	Wet work, handwashing, detergents, soaps, disinfectants, gloves, solvents, friction, occupational exposure
Interdigital spaces	Highly susceptible because of the thin epidermis and frequent occlusion. Interdigital dermatitis can be an early sentinel sign in hairdressers.	Shampoo, hair dyes, bleaching agents, wet work, occlusion, detergent residue
Eyelids/periorbital skin	Even limited exposure can cause prominent erythema, burning, stinging, scaling, or edema because eyelid skin is thin and highly permeable. Hand-to-eyelid transfer is common.	Eye cosmetics, mascara solvents, cleansers, airborne particles, nail products transferred by hand
Face	May resemble ACD, rosacea, seborrheic dermatitis, or photodistributed dermatitis. Burning and stinging may be prominent.	Cosmetics, sunscreens, retinoids, hydroxy acids, masks, cleansers, shaving products, airborne agents
Lips/perioral area	Irritant contact cheilitis occurs more often than allergic cheilitis, with sharply bordered perioral erythema, scaling, cracking, burning, or soreness.	Saliva, lip licking, toothpaste, mouthwash, spicy foods, lip cosmetics, musical instruments
Scalp	May cause burning, stinging, pruritus, erythema, scaling, erosions, or oozing after hair-care product exposure. Because the scalp is hair-bearing and seborrheic dermatitis is common, ICD may go unrecognized or be mistaken for seborrheic dermatitis, psoriasis, or ACD.	Shampoos, hair dyes, bleaching agents, permanent-wave solutions, relaxers, alcohol-containing tonics, exfoliating scalp products, prolonged product contact
Vulva/genital skin	Hydration, occlusion, friction, and high permeability facilitate vulvar ICD, which may cause burning, soreness, erythema, fissuring, or erosions.	Urinary incontinence, excessive hygiene, wipes, occlusive underwear, bidet
Perianal area	May cause burning, soreness, erythema, maceration, or fissuring. Infection or inflammatory dermatoses can coexist with chronic irritation.	Fecal soiling, diarrhea, wipes, cleansers, topical hemorrhoid preparations, occlusion
Feet	May affect the dorsal feet, interdigital areas, or soles. Hyperkeratotic ICD can develop at weight-bearing or friction-prone sites.	Occlusive footwear, sweating, friction, detergents, topical medications, occupational exposure

Adapted and expanded from Bains et al. [2], incorporating additional information from Ale and Maibach [17].
ICD, irritant contact dermatitis; ACD, allergic contact dermatitis.

independently diagnostic. Histopathological distinction between chronic ICD and ACD is generally unreliable.

The broad differential diagnosis of ICD should be guided by anatomical site and morphology. Conditions that can mimic ICD include ACD, AD, psoriasis, dyshidrotic eczema, tinea manuum or tinea pedis, nummular eczema, and cutaneous infection [2]. Because ICD and ACD often coexist, evaluation should identify all relevant irritant and allergic contributors rather than simply assign one label. Treatment can then combine irritant reduction, barrier repair, and targeted allergen avoidance.

Relation to allergic contact dermatitis

Mechanistic interplay: irritant contact dermatitis as a precursor to allergic contact dermatitis

ICD and ACD are linked mechanistically as well as diagnostically. Nedorost [24] proposed that the allergen strength needed for sensitization depends on the underlying skin condition. In healthy skin, only strong allergens capable of acting as irritants themselves, such as para-phenylenediamine, can induce ACD [24]. By contrast, chronic inflammation or barrier impairment permits sensitization even to weak or moderately potent allergens [24,25]. This difference has been attributed to predominantly T helper 1-skewed responses in healthy skin versus T helper 2-skewed responses in chronically inflamed skin [24].

Clinical evidence supports this relationship: barrier impairment due to AD or wet work is associated with greater susceptibility to contact sensitization by less potent allergens. Kohli and Nedorost [25] found that childhood-onset flexural dermatitis predisposed patients to contact allergy to weak sensitizers, whereas current wet work predisposed them to allergy to moderate sensitizers. Neither factor was associated with sensitization to strong sensitizers [25]. Thus, ICD may do more than mimic ACD: it may create an inflammatory environment with a disrupted barrier that facilitates subsequent allergic sensitization.

Clinical example: rubber glove allergy

Rubber glove allergy illustrates the interaction between ICD and ACD. Workers with pre-existing ICD from frequent wet work, hand hygiene, or cleaning agents may wear protective gloves more often, increasing their exposure to rubber additives. With an already impaired barrier, they may subsequently become sensitized to rubber accelerators such as thiurams, carbamates, thiazoles, thioureas, and guanidines and develop ACD [26]. This sequence is particularly relevant in occupations such as healthcare, where glove use, wet work, and repeated hand hygiene often coexist [26].

Thiurams and carbamates have long been important rubber ac-

celerator allergens. Carba mix and diphenylguanidine have also become increasingly relevant, particularly with synthetic rubber gloves [26]. Affected patients should avoid the offending gloves and choose alternatives, such as accelerator-free nitrile or polyvinyl chloride/vinyl gloves, according to workplace protection requirements [26]. ICD and ACD are therefore not mutually exclusive. In chronic, recurrent, or occupational dermatitis, particularly of the hands, clinicians should assess both irritant exposure and allergic sensitization [16,19,27].

Occupational aspects and hand eczema

Wet work and occupational exposures

ICD is the most common form of OSD, and the hands are affected most often because of repeated workplace irritant exposure [4,11]. A recent systematic review and meta-analysis found moderate-quality evidence identifying wet work as an important risk factor for occupational ICD [4]. The standard definition of wet work requires at least one of the following during a working day: wet hands for more than 2 hours, more than 20 handwashing episodes, or occlusive glove use for more than 2 hours [28]. These exposures increase stratum corneum hydration and skin permeability, extract lipids and NMF, and impede barrier recovery, lowering the threshold for irritant-induced inflammation [2,29].

Wet work rarely occurs alone. Workplace water exposure often accompanies exposure to soaps, detergents, disinfectants, or other irritants. Occlusion, friction, pressure, and repeated minor trauma further damage the epidermal barrier, while heat, sweating, cold, low humidity, and poor ventilation may intensify irritation [2,11,29]. This cumulative pattern explains why occupational ICD often develops gradually as chronic cumulative hand eczema rather than after a single acute irritant exposure.

High-risk occupations

Table 3 summarizes occupations at particularly high risk of ICD, including hairdressers, food service workers, healthcare workers, metalworkers, and cleaners [29,30]. Their shared exposures include repeated wet work, frequent hand hygiene, detergents or disinfectants, alkaline or solvent-based materials, glove occlusion, and repetitive mechanical trauma.

Hairdressers are a well-recognized high-risk group. Interdigital dermatitis often develops early in their apprenticeship and is considered a sentinel event preceding more severe hand dermatitis [11]. This early involvement of the web spaces reflects repeated exposure to shampoo, water, hair dyes, bleaching agents, and glove occlusion. Prompt recognition matters because timely education and exposure modification may prevent progression to chronic occupational hand eczema.

Protective strategies: gloves and barrier measures

Prevention and management depend on reducing irritant exposure while maintaining occupational protection. Measures include substituting irritants, limiting wet work, drying hands thoroughly, using moisturizers, and wearing appropriate protective equipment [2,11].

Gloves are essential for protection against irritants, but prolonged occlusion can itself impair the barrier and increase susceptibility to irritation [31]. Experiments help clarify this damage. Wearing occlusive gloves for 6 hours daily over 3 days did not significantly impair barrier function in normal skin, but significantly worsened it in skin previously irritated with SLS [32]. After 6 hours of daily glove wear for 2 weeks, even normal skin showed significant barrier impairment, indicated by increased TEWL [32]. These findings suggest that occlusion may be particularly harmful to an already compromised barrier and that glove-wear

Table 3. High-risk occupations and common irritant exposures in occupational irritant contact dermatitis

Occupation	Major irritants and exposure patterns
Healthcare workers	Frequent handwashing, alcohol-based hand rubs, soaps, disinfectants, chlorhexidine, detergents, prolonged glove occlusion, sweating under gloves
Hairdressers	Wet work, shampoos, detergents, hair dyes, bleaching agents, permanent-wave solutions, thioglycolates, persulfates, glove occlusion
Food service workers/cooks	Wet work, soaps, detergents, food juices, spices, acids, alkalis, repeated handwashing, glove occlusion
Butchers/fishmongers	Wet work, animal proteins, blood, brine, detergents, disinfectants, cold exposure, glove occlusion, friction from tools
Cleaners/housekeeping workers	Detergents, surfactants, disinfectants, bleach, ammonia, solvents, frequent wet work, glove occlusion
Metalworkers/machinists	Cutting oils, metalworking fluids, coolants, solvents, degreasers, metal particles, friction, occlusive gloves
Construction workers/cement workers	Wet cement, alkaline materials, chromate-containing cement, dust, solvents, friction, trauma, cold or heat exposure
Beauticians/nail technicians	Solvents, acetone, acrylates, nail products, detergents, disinfectants, cosmetics, repeated handwashing
Dental workers	Frequent hand hygiene, disinfectants, acrylics, impression materials, glove occlusion, wet work
Agricultural workers/florists	Plant sap, soil, fertilizers, pesticides, wet work, mechanical trauma, cold exposure

Adapted and revised from Ale and Maibach [30].

duration has clinical importance.

Cotton glove liners may lessen the adverse effects of prolonged occlusion by absorbing sweat, reducing friction, and improving comfort. They reduced barrier impairment from prolonged glove wear in the long-term occlusion model [32]. Cotton liners should therefore be considered for workers who need prolonged occlusive glove use, especially those with pre-existing ICD, AD, or chronic hand eczema (CHE).

Barrier creams and moisturizers are adjuncts to, rather than substitutes for, gloves and exposure reduction. Moisturizers help restore stratum corneum hydration and barrier function. Barrier creams may provide partial protection against selected irritants, but are often inadequate for intense or prolonged exposure [11].

Workplace assessment

Workplace assessment can help when occupational ICD is suspected, especially in chronic, recurrent, or severe cases. A detailed occupational history should identify potential workplace irritants and allergens, establish how exposure relates temporally to onset or exacerbation, and determine whether symptoms improve away from work [33]. Evaluation should directly assess the worker's tasks, wet-work duration, handwashing, PPE, and opportunities to reduce or substitute exposures [4,34,35]. Product labels and material safety data sheets (MSDS) should also be reviewed to identify possible irritants and recommended precautions [33]. MSDS require cautious interpretation because they may omit clinically relevant irritants [35].

Persistent post-occupational dermatitis

Persistent post-occupational dermatitis (PPOD) persists or recurs long after occupational exposure has ended [36]. It challenges the assumption that removing exposure necessarily leads to complete resolution. Barrier dysfunction and inflammatory susceptibility can persist for years, particularly after severe, prolonged, or recurrent occupational hand dermatitis [36]. Patients should be told that improvement may be slow even after exposure reduction or a job change and that long-term protection and maintenance therapy may remain necessary. PPOD reinforces the occupational-health need for early recognition, prompt exposure control, and prevention before dermatitis becomes chronic. Clinicians should consider it when counseling patients whose dermatitis began at work and who continue to have persistent or recurrent eczema resembling endogenous dermatitis [36].

Prevention and treatment

Barrier recovery kinetics

Epidermal barrier recovery after ICD takes considerably longer than is generally recognized. In human experimental models using SLS, complete recovery from acute ICD took approximately 4 weeks [37]. In a chronic model, 1% SLS was applied for 30 minutes daily for 5 days, with this schedule repeated over 3 consecutive weeks. Previously irritated sites remained hyperreactive even 10 weeks later, indicating that biophysical markers may take a long time to normalize [38].

Recovery also depends on the surfactant. In detergent patch tests, SLS caused persistent, concentration-dependent TEWL increases even 10 days after exposure, whereas sodium laureth sulfate allowed faster recovery and alkyl polyglucoside caused little detectable irritation [39]. Undetectable irritation does not mean an absence of irritant potential: even mild surfactants may cause irritation with repeated or prolonged exposure [39]. Because recovery is prolonged, renewed irritant exposure before full barrier restoration is a key mechanism in progression from acute or subclinical irritation to chronic cumulative ICD.

Irritant avoidance and skin protection

Prevention underpins ICD management. The 4R principle organizes practical care into 4 actions: recognize the causative irritant, remove it from the patient's environment, reduce inflammation, and restore the skin barrier [40]. Recognition requires detailed assessment of occupational, domestic, and recreational exposures, including the irritant, exposure frequency and duration, work practices, and PPE use [2,11,40]. Patch testing should be performed if concomitant ACD is suspected [1,16,40]. Removal means eliminating the irritant from the workplace and home wherever feasible [40]. If complete avoidance is impractical, particularly in occupational ICD, clinical benefit may still come from reducing exposure frequency, duration, or intensity and substituting less irritating products [11,40].

Reducing inflammation requires treatment tailored to the acuity, severity, morphology, and anatomical site of active dermatitis [40]. Anti-inflammatory therapy may be needed when irritant avoidance is insufficient, particularly in persistent ICD or with coexisting endogenous dermatosis such as AD; it nevertheless remains secondary to adequate exposure control [2,16,40]. Restoration requires continued skin protection and appropriate basic topical therapy to help the damaged epidermal barrier recover [40]. Because clinical improvement may precede full functional recovery, protective measures and regular use of a suitable moisturizer should continue after visible dermatitis resolves [37-40].

Barrier-restorative products should be selected individually: effects vary by formulation and irritant, and some products may paradoxically increase susceptibility [40].

Moisturizers and barrier restoration

Both prevention and treatment rely on moisturizers. Emollients such as lanolin, fatty acids, cholesterol, and ceramides fill gaps between corneocytes to smooth the skin. Occlusives, including petrolatum, mineral oil, and silicones, reduce water loss by forming a hydrophobic film. Humectants such as glycerin and urea draw water into the stratum corneum. Many formulations combine these functions. Lipid-rich, fragrance-free moisturizers with low irritant potential are recommended for occupational ICD and CHE [2,11]. Greasy preparations rich in lipids or free fatty acids may be particularly helpful for barrier restoration.

Anti-inflammatory agents

Topical corticosteroids (TCS) have a more limited and less consistent role in ICD than in ACD or AD. Reviews covering acute and chronic ICD found a consistent lack of significant TCS efficacy in experimental models [41]. One proposed explanation is that their antiproliferative effects and suppression of epidermal lipid synthesis may impede barrier recovery despite their anti-inflammatory action. Short-term glucocorticoid treatment has been shown to compromise permeability barrier homeostasis and stratum corneum integrity by inhibiting epidermal lipid synthesis [42]. TCS should therefore not be considered primary barrier-restorative treatment for ICD.

Topical calcineurin inhibitors (TCIs), including tacrolimus and pimecrolimus, have also been investigated; these agents inhibit calcineurin-dependent T-cell activation and reduce inflammatory cytokine production [43]. Repeated TCI application in experimental studies compromised stratum corneum integrity, epidermal permeability, and antimicrobial barrier function to an extent comparable to TCS [44]. Applying tacrolimus after SLS irritation has been shown to increase inflammation [16]. Pimecrolimus, however, has a more cell-selective pharmacological profile, downregulates proinflammatory mediators such as TNF-α and IL-8, and has shown anti-inflammatory activity in the SLS irritation test [43,45]. It may therefore be considered when sensitive sites require anti-inflammatory treatment.

Systemic and advanced therapies

Systemic or advanced therapies have limited use in uncomplicated ICD, which is sustained primarily by direct barrier injury rather than a systemic immune-mediated process [2,16]. Systemic anti-inflammatory treatment is rarely needed for pure ICD, and robust controlled clinical evidence does not support its use. It may be considered when ICD is part of severe refractory CHE, but this should not be interpreted as ICD-specific treatment.

Alitretinoin has the strongest support among systemic agents for severe refractory CHE. Korean clinical studies and real-world data indicate that it can be effective and generally well tolerated in moderate-to-severe CHE [46-48]. CHE is heterogeneous, however, and can include irritant, allergic, atopic, hyperkeratotic, and endogenous components [49]. Cyclosporine, methotrexate, and azathioprine have also been used off-label for severe CHE, but ICD-specific evidence is limited [49]. These agents should therefore be reserved for selected cases in which ICD forms part of a severe CHE phenotype, after ongoing irritant exposure and clinically relevant allergic sensitization have been carefully excluded.

Oral antihistamines do not directly address ICD pathophysiology, which is driven mainly by barrier disruption and innate inflammatory activation rather than histamine-mediated inflammation [2,16]. They should therefore not be considered disease-modifying treatment for ICD. Sedating agents may serve only as symptomatic adjuncts for sleep disturbance or prominent itch. Evidence for dupilumab is emerging in chronic recalcitrant hyperkeratotic ICD and CHE [11,50]. Further studies are needed to determine its efficacy in ICD; it is not yet an established treatment for pure ICD.

Phototherapy may be an adjunct for cumulative ICD through enhancement of skin barrier function by repeated low-level ultraviolet exposure [11]. In one study of eczematous hand dermatitis that included patients with ICD, both psoralen–ultraviolet A and narrowband ultraviolet B phototherapy were associated with clinical improvement [16]. More than half of the patients relapsed after treatment stopped, however, suggesting an adjunctive role and a possible need for maintenance therapy [16]. Overall, systemic and advanced therapies remain exceptional, adjunctive, or investigational options for ICD; treatment should continue to prioritize exposure reduction, skin protection, and barrier restoration.

Conclusion

ICD is the most common type of CD and the most frequent presentation of OSD. It is a distinct inflammatory disorder driven by barrier dysfunction and mediated by innate immunity, with its own pathophysiology, clinical spectrum, occupational relevance, and treatment principles. It should therefore be recognized as more than a diagnosis reached after ACD has been excluded.

Advances in ICD research have extended understanding beyond simple barrier damage. CCL2–CCR2 signaling, TLR3 activation, and inflammasome-related IL-1 family cytokine signaling

are being clarified within the broader context of epidermal barrier disruption and innate immune activation [5,7,8]. AD and other host determinants of barrier susceptibility further influence individual risk [2,4]. Clinical presentations range from subjective sensory irritation and suberythematous barrier damage to acute, chronic cumulative, occupational, airborne, and site-specific forms [2,16]. Wet work remains the most important occupational exposure, and accurate risk assessment and protective strategies such as cotton glove liners can help prevent disease [4]. The 4R principle summarizes management: recognize, remove, reduce, and restore [40].

Future research should convert mechanistic and diagnostic advances into clinical tools. RCM and molecular biomarker panels need validation in real-world populations with overlapping ICD, ACD, AD, and CHE. Studies should also clarify the role of dupilumab and other targeted therapies in recalcitrant ICD. These developments may improve the precision of diagnosis, prevention, and management for this common, underrecognized condition.

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Korean Standard Series allergens and emerging sources: a narrative review

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Purpose: This study aimed to address gaps in Korean Standard Series (KSS) information, highlight allergens with increasing patch test positivity, describe potential sources encountered in daily life, and provide guidance on selecting allergen-free alternatives.

Methods: Relevant information was identified from KSS patient instruction sheets (Chemotechnique, Sweden), T.R.U.E. TEST patient instruction sheets (SmartPractice, United States), the Contact Dermatitis Institute allergen database, the American Contact Dermatitis Society allergen information sheets, and searches of the PubMed database. English-language review articles, case series, and case reports identified using keywords related to the 25 KSS allergens were selected.

Results: Information was updated for the following allergens: nickel, cobalt, potassium dichromate, balsam of Peru, paraben mix, *N*-isopropyl-*N*'-phenyl-*p*-phenylenediamine, formaldehyde, *p-tert*-butylphenol formaldehyde resin, methylchloroisothiazolinone/methylisothiazolinone, colophonium, imidazolidinyl urea, and 2-mercaptobenzothiazole. Emerging sources included electronic devices, personal protective equipment, including masks whose use increased during the COVID-19 (coronavirus disease 2019) pandemic, nail products, and children's toy slime. In addition, occupational allergen information sheets were developed for hairdressers, healthcare workers, dentists, dental hygienists, and cooks. The Korean-language allergen sheets are provided in the Supplementary Materials.

Conclusion: Because the KSS has not been revised for more than 2 decades, emerging allergen sources may be inadequately represented in the existing patient information. Accordingly, updated patient instruction sheets were developed to improve patient understanding and facilitate the practical application of patch test results.

Keywords: Allergens; Allergic contact dermatitis; Guideline; Patch tests; Patient education

Introduction

Background

Patch testing is essential for identifying allergens responsible for allergic contact dermatitis (ACD) and guiding allergen avoidance through appropriate lifestyle modifications. However, existing allergen information sheets may omit emerging sources of exposure and may be difficult for patients to interpret, potentially limiting their understanding of patch test results. Clear patient education is important because patients may have difficulty recalling their patch test results and the specific allergens they should avoid over time [1].

Objectives

This review summarizes contact allergens, cross-reactors, and relevant dietary restrictions associated with the 25 allergens included in the Korean Standard Series (KSS), with an emphasis on exposures encountered in daily life.

Methods

Ethics statement

Because this study was based exclusively on published literature and other publicly available information, institutional review board approval and informed consent were not required.

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Study design

This narrative review was based on a search of the academic literature and other relevant information sources.

Information sources and search strategy

A comprehensive literature search was conducted to identify emerging sources, cross-reactors, and occupational exposure risks associated with the 25 allergens included in the KSS. The primary academic literature search was conducted in PubMed using combinations of terms specific to the 25 KSS allergens together with terms such as "allergic contact dermatitis," "allergen sources," and "cross-reactivity."

To support patient education, established patch test databases and commercially available patient instruction materials were reviewed alongside the academic literature. These sources included the KSS patient instruction sheets [2] (Chemotechnique, Sweden), T.R.U.E. TEST patient instruction sheets [3] (SmartPractice, United States), the Contact Dermatitis Institute allergen database [4], and the American Contact Dermatitis Society allergen information sheets [5].

Selection process

The academic literature was limited to English-language review articles, case series, and case reports. Studies were selected if they described recent trends in everyday allergen exposure, including exposures associated with modern electronic devices, personal protective equipment, and cosmetics. Publications describing specific dietary restrictions and occupational exposure risks were also included. Information from the selected sources was synthesized to develop an updated guide for patient education and allergen avoidance.

Results

KSS allergens

The allergens are presented in order of patch test positivity rates, as reported by Kwon et al. [6]. Table 1 summarizes the allergens and their sources, and Table 2 summarizes emerging sources [7-46]. The Korean-language allergen sheets are provided in the Supplement 1.

Nickel (II) sulfate hexahydrate

Nickel is widespread in the modern environment and reportedly causes contact dermatitis more frequently than other metals. Common sources include everyday metallic items such as coins, keys, paper clips, needles, tools, and lighters. Nickel is also present in faucets, kitchen utensils, washing machines, tumblers, and electronic devices, including cell phones, laptops, tablets, AirPods, and smartwatches [7-9]. Reactions may be more pronounced in moist conditions, such as after sweating. Prolonged contact between water and a metal pot may increase nickel release, so it is advisable to replace the water after each use. Additional sources include razors, eye cosmetics, tattoo inks—particularly green and blue inks and, less commonly, brown and violet inks—nail polish, and nail tips or stickers [10-13]. Fashion items, including watches, eyeglass frames, zippers, buttons, belt buckles, and jewelry made of white gold, 14K gold, chrome, copper, or tin, may also contain nickel. Orthopedic and dental prostheses, such as dental braces, as well as insulin pumps and blood glucose meters, may contain nickel [14,15]. Industrial sources include pesticides, paint pigments, putty, catalysts, wires, and machinery.

Patients are advised to avoid soy products (e.g., soy milk, miso, and tofu), nuts (e.g., almonds and peanuts), cereals, vitamin supplements, and chocolate products. Meat may be preferable to seafood, such as shrimp and clams [47]. Smoking cessation is strongly advised because cigarettes contain nickel. Direct contact with metal items in daily life should be minimized; unavoidable objects, such as doorknobs, may be covered with fabric. Potentially safer alternatives include aluminum, gold, silver, and platinum. Although stainless steel contains nickel, allergic reactions are uncommon because it generally releases only small amounts. Nevertheless, nonstick-coated cookware is considered preferable to stainless-steel cookware. Co-sensitization may occur with palladium, cobalt, chromium, and other metals.

Cobalt (II) chloride hexahydrate

Cobalt is present in metallic items such as keys, magnets, zippers, buttons, belt buckles, jewelry, and tools, as well as in electronic devices such as cell phones. It is also found in light-brown pigments used in products such as hair dyes and tinted cosmetics; blue pigments used in tattoos, inks, and porcelain glazes; glass; and nail tips or stickers [13]. In industrial settings, cobalt salts may be encountered in bricks, wet cement, paint, tire manufacturing, plastic processing, welding, and animal feed.

Patients may be advised to avoid foods containing whole grains (e.g., flaxseed), legumes (e.g., chickpeas), nuts, apricots, beets, cabbage, beer, tea, coffee, cocoa, chocolate, cloves, liver, and scallops, as well as vitamin B12 supplements. Orthopedic and dental prostheses may also contain cobalt. Silver and stainless-steel products may be suitable alternatives. Small items such as keys can be coated with nail polish, whereas larger items such as scissors can be coated with plastic. Co-sensitization may occur with other metals, including nickel and chromium.

Table 1. Overview of the Korean Standard Series allergens and their sources

No.	Allergen	Personal care products	Clothing or jewelry	Medical products	Rubber products	Cleaning products	Industrial products
1	Nickel		V				V
2	Lanolin	V	V	V		V	V
3	Neomycin sulfate			V			V
4	Potassium dichromate		V	V			V
5	Mercury ammonium chloride	V		V			V
6	Fragrance mix I	V		V		V	V
7	Colophonium	V		V		V	V
8	Imidazolidinyl urea	V		V		V	V
9	Clioquinol	V		V		V	V
10	Balsam of Peru	V		V		V	V
11	IPPD		V		V		V
12	Cobalt		V				V
13	PTBP	V	V			V	V
14	Paraben mix	V		V			V
15	Captan	V					V
16	Budesonide	V		V			V
17	MCI/MI	V		V		V	V
18	Quaternium-15	V		V		V	V
19	MBT		V	V	V		V
20	PPD	V	V		V		V
21	Formaldehyde	V	V			V	V
22	Mercapto mix		V	V	V		V
23	Thimerosal	V		V			V
24	Thiuram mix		V	V	V		V
25	Tixocortol-21-pivalate	V		V			

IPPD, *N*-isopropyl-*N*′-phenyl-p-phenylenediamine; PTBP, *p*-*tert*-butylphenol formaldehyde resin; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MBT, 2-mercaptobenzothiazole; PPD, *p*-phenylenediamine.

Potassium dichromate

Potassium dichromate has various industrial applications and may be encountered in stainless steel items, including tools, watches, rings, earrings, bracelets, and belts, as well as in orthopedic and dental prostheses and surgical catgut sutures. Additional sources include sterling silver (925 silver), detergents, cosmetics, nail tips or stickers, green pigments used in products such as tattoo inks and porcelain glazes, and photographic developers [13]. Potassium dichromate is also used in leather tanning and may therefore be present in leather goods and furs, including footwear, gloves, steering wheels, and handbags. Vegetable-tanned leather may provide an alternative.

Dietary recommendations include avoiding apple peels, canned fruits, grapes, potatoes, meat, nuts, chocolate, spices, tea, wine, beer, multivitamins, and chromium picolinate supplements. In occupational settings, exposure to sand, matches, ash, treated wood, wet cement, and mortar should be minimized. Alternatives include cement with reduced dichromate content or cement supplemented with ferrous sulfate. Metalworking fluids should be changed regularly during machining operations.

Balsam of Peru (Myroxylon pereirae resin)

Balsam of Peru, an aromatic resinous liquid, is used as a fragrance or flavoring component in products such as air fresheners, deodorants, candles, mouthwashes, toothpastes, shampoos, soaps, moisturizers, fragrances, essential oils, aromatherapy products, diapers, and baby powders. It may also be present in ointments, dressings, dental adhesives, pesticides, insect repellents, and scented tobacco products.

Foods and flavorings that may need to be avoided include allspice, cinnamon, vanilla, citrus products, paprika, nutmeg, cloves, curry, chili sauce, ketchup, tomatoes, pickles, pastries, sweets, ice cream, candy, chewing gum, chocolate, soft drinks, and alcoholic beverages [14]. Products labeled as "unscented" may still contain masking fragrances related to Balsam of Peru. Potential cross-reactors include fragrance mix, cedarwood, musk, orange peel extract,

Table 2. Allergens with emerging sources

Allergen	Sources
Nickel	• Diabetes-related medical devices (glucose sensors, insulin pumps) [15], stainless steel skull pins [40], metal dental braces [41], nitinol stent graft (rarely) [42]
	• Metallic hairdressing tools (tweezers, sectioning clips, hair clips, straight razors, crochet hooks, tail combs) [37]
	• Tattoo inks (green, blue > brown, violet) [11]
	• Microblading eyebrow tattooing [43]
	• Eyebrow pencil [10]
	• Mobile phones, laptop computers, video game controllers [7], AirPods [8], smartwatches (e.g., Apple Watch) [9]
	• Nail tips and nail stickers [13], nickel mixing beads in nail polish [12]
	• Dance poles [44]
	• Piercings [14]
	• Figs, raspberries [14]
Potassium dichromate	• Nail tips and nail stickers [13]
Colophonium	• Diabetes-related medical devices (adhesives for glucose sensors, insulin pumps) [15]
	• Medical adhesives (adhesive tapes, adhesive bandages, and suture adhesives) [35]
	• Safety illustration printed on medical devices [45]
	• Wearable health devices [33]
	• Beeswax wraps [46], depilatory wax [16]
	• Disposable paper napkins [38]
	• Christmas trees [39]
	• Sanitary pads [34]
Imidazolidinyl urea	• Ultrasound gels [32]
Balsam of Peru	• Cookies, tomatoes, ice cream, chutney, cola, ketchup, chocolate, alcoholic beverages [14]
IPPD	• Black rubber vehicle handbrake handles [20]
	• Galaxy Fit strap [19]
	• Gas masks [21]
Cobalt	• Metallic hairdressing tools (tweezers, sectioning clips, hair clips, straight razors) [37]
	• Nail tips and nail stickers [13]
PTBP	• Artificial nails [29]
	• Athletic tape [29]
	• Swimming goggles [27]
	• Basketballs [28]
Paraben mix	• Strawberries, blueberries, grapes, olives, yeast, barley [18]
	• Children's toy slime [17]
MCI/MI	• Children's nail polish [30]
	• Cosmetic glitter adhesive [31]
	• Children's toy slime [17]
	• Ultrasound gels [32]
MBT	• Elastic diaper edges [36]
Formaldehyde	• Eyelash adhesives [22]
	• Nail hardeners [12]
	• Tattoo inks [24]
	• Cigarette smoke [23]
	• Backpack shoulder straps [25]
	• Surgical polypropylene N95 (FFP2) respirators [26]
	• Cod, caviar, coffee, shiitake mushrooms, smoked ham, maple syrup, aspartame [14]

IPPD, *N*-isopropyl-*N*'-phenyl-*p*-phenylenediamine; PTBP, *p*-*tert*-butylphenol formaldehyde resin; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MBT, 2-mercaptobenzothiazole.

propolis, beeswax, turpentine, tolu balsam, copaiba balsam, rosin, wood tar, *Krameria triandra*, coumarin, and diethylstilbestrol.

Thimerosal

Thimerosal, which is now rarely used, was previously a common antiseptic in medical products and has largely been replaced by other preservatives. It may still be present in some contact lens solutions, vaccines, antitoxins, disinfectants, cosmetics, and cleansing products and has also been used as a fluorescent dye in forensic applications.

Patients with thimerosal allergy should inform their healthcare providers; however, medically indicated vaccination should not be delayed solely because of this allergy. Many vaccines intended for young children are thimerosal-free, and although some adult vaccines may contain thimerosal, thimerosal-free alternatives are often available.

Fragrance mix I

Fragrance mix I contains cinnamyl alcohol, cinnamaldehyde, amyl cinnamaldehyde, hydroxycitronellal, geraniol, eugenol, isoeugenol, and oakmoss absolute. These substances are commonly used as fragrance ingredients in air fresheners, deodorants, incense, candles, detergents, fabric softeners, mouthwashes, toothpastes, shampoos, soaps, moisturizers, perfumes, essential oils, and herbal or botanical products. Products marketed as unscented may contain fragrance ingredients used to mask other odors. Components of fragrance mix I or related fragrance substances may also be encountered in ointments, disinfectants, dental cement, pesticides, paper products, and scented tobacco. When selecting topical products, patients should also be aware of ingredients such as propolis, tea tree oil, and other plant-derived oils.

Related fragrance and flavoring substances may also be used in candy, ice cream, chewing gum, and soft drinks. Patients with clinically significant fragrance allergy may need to avoid cinnamon, cloves, vanilla, and citrus flavorings, including citrus peel. Cross-reactions may occur with Balsam of Peru, daffodil, sandalwood oil, and citronella.

Paraben mix

Parabens are widely used preservatives in personal care products such as shampoos, soaps, and moisturizers, as well as in toothpastes, cosmetics, quick-drying nail polish, hair dyes, certain fabrics, and children's toy slime [17]. They may also be present in bandages, local anesthetic preparations, and topical medications. Some individuals with positive patch test reactions to parabens may tolerate paraben-containing products; however, products associated with a skin reaction should be discontinued.

Parabens may be used as preservatives in foods such as mayonnaise, salad dressings, ketchup, hot sauce, mustard, processed fruits and vegetables (e.g., olives), dairy products, baked goods, jellies, jams, soft drinks, syrups, and candy [18]. Ingestion of foods containing permitted parabens as preservatives is generally considered safe.

N-isopropyl-N'-phenyl-p-phenylenediamine

N-isopropyl-*N*'-phenyl-*p*-phenylenediamine (IPPD) is an antioxidant used in rubber manufacturing and is present in black rubber products such as smartwatch straps, disposable mask straps, handle grips on cookware, exercise equipment, and vehicle handbrakes, sports tape, shoe insoles, and rubber gloves [19,20]. It may also be present in photographic materials and printer inks. Occupational sources include grease, lubricants, gasoline, gas masks, automobile tires, and brake linings [21]. IPPD may cross-react with *p*-phenylenediamine (PPD), a common ingredient in hair dye.

Tixocortol-21-pivalate

Tixocortol-21-pivalate is a group A corticosteroid used in topical preparations. Cross-reactivity may occur with other corticosteroids, including budesonide (Pulmicort), desonide (DesOwen), fludrocortisone, hydrocortisone (LactiCare), triamcinolone, methylprednisolone (Advantan), prednisolone (Lidomex), and prednicarbate (Dermatop).

Formaldehyde

Formaldehyde is widely used as a preservative, disinfectant, and industrial chemical and may be present in hair products, cosmetics, nail polish, nail hardeners and removers, eyelash adhesives, fabrics, and pottery glazes [12,22]. Other reported sources include tobacco smoke, photographic developers, tattoo inks, and backpack shoulder straps [23-25]. To reduce exposure from clothing, newly purchased garments may be washed several times in hot water before use, and wrinkle-resistant clothing may be avoided when relevant.

Foods reported to contain formaldehyde include cod, caviar, shiitake mushrooms, smoked ham, maple syrup, aspartame-containing products, coffee, and chewing gum [14]. Occupational and environmental sources include N95 respirators, wood smoke, exhaust fumes, paint, pesticides, fungicides, adhesives, plywood, coolants, and insulating materials [26]. Cross-reactions may occur with formaldehyde-releasing preservatives such as quaternium-15, bronopol, dimethylol dimethyl hydantoin, diazolidinyl urea, and imidazolidinyl urea.

p-Phenylenediamine

PPD is present in hair dyes, black rubber products, black pigments used in products such as henna preparations, printer inks, lithographic materials, and photographic developers, and black-dyed fabrics, furs, and footwear. Occupational sources may include grease, oils, and gasoline. Patients are advised to avoid relevant dyed clothing, fabrics, and furs because of possible reactions to related dyes containing phenylenediamine compounds. Cross-reactions may occur with aniline yellow, disperse orange dyes, and *p*-toluenediamine.

Mercury ammonium chloride

Mercury compounds have historically been used as fungicides and antiseptics and may be encountered in products such as disinfectants (e.g., Mercurochrome), skin-lightening creams, mascara, dental amalgam, fluorescent lamps, batteries, and scientific instruments such as thermometers, barometers, and liquid-mirror telescopes. However, the use of mercury-containing products has declined globally following implementation of the Minamata Convention. Seafood may nevertheless contain trace amounts of mercury.

Thiuram mix

Thiuram mix contains tetramethylthiuram disulfide, tetramethylthiuram monosulfide, and tetraethylthiuram disulfide. Thiurams are used as rubber accelerators and may be present in rubber gloves, bands, mats, handle grips, electrical cords, earphones, erasers, makeup sponges, goggles, swimwear, wetsuits, tires, masks, tubing, hoses, and some soaps. Medical sources include stethoscopes, tourniquets, dental rubber dams, and condoms. Occupational exposure may occur through pesticides and fungicides as well as through the manufacture or handling of tires, masks, tubing, and hoses.

Patients with thiuram allergy should avoid relevant natural and synthetic rubber products and use vinyl, plastic, leather, wood, or fabric alternatives when feasible. If contact with an allergen-containing item cannot be avoided, a physical barrier such as fabric or plastic film may reduce direct skin contact. Patients should also be aware of possible reactions to disulfiram, a medication used to treat alcohol dependence.

Neomycin sulfate

Neomycin is a topical aminoglycoside antibiotic found in products such as Madecassol. Cross-reactions may occur with other aminoglycoside antibiotics, including butirosin, framycetin, mycifradin, gentamicin, kanamycin, streptomycin, sisomicin, spectinomycin, paromomycin, and fradiomycin. Concomitant allergy to bacitracin (Baspo) may also occur. Alternative topical agents that do not contain neomycin include mupirocin preparations such as Bactroban and Esroban and povidone-iodine products such as Betadine.

p-tert-Butylphenol formaldehyde resin

p-tert-Butylphenol formaldehyde resin (PTBP) is used primarily as an adhesive in leather and rubber products. Reported sources include disposable masks, sports tape, swimming goggles, basketballs, deodorants, lip liners, artificial nails, nail adhesives, shoes, belts, and handbags [27-29]. PTBP may also be present in furniture adhesives, billiard balls, pesticides, electrocardiogram electrode adhesives, bandages, dental bonding materials, printer inks, photographic developers, and copy paper.

Patients should avoid PTBP-containing waterproof adhesives used in leather goods. Frequent changes of socks and keeping footwear dry may help reduce dermatitis associated with exposure from footwear. In occupational settings, exposure to PTBP-containing plywood, laminated wood, fiberglass, mineral fiber products, sealants, coatings, and insulating materials should be minimized.

Methylchloroisothiazolinone/methylisothiazolinone

Methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) is a preservative mixture used in a variety of household and personal care products, including detergents, fabric softeners, wipes, coated paper products, soaps, body washes, shampoos, conditioners, toothpaste, and mouthwashes. MCI and/or MI may also be present in nail polish, cosmetic glitter adhesives, toy slime, paints, ultrasound gels, and printer inks [17,30-32]. In occupational settings, exposure may occur through paints, metalworking fluids, and adhesives.

In Korea, the United States, Canada, Europe, and other countries, the use of MI or MCI/MI mixtures is restricted; these restrictions include a concentration limit of 0.0015% in rinse-off products and prohibitions in certain other products, such as leave-on cosmetics. Toothpastes containing these preservatives have also been banned in Korea.

Budesonide

Budesonide is a group B steroid used topically. Patients with budesonide allergy should inform their healthcare providers and avoid medications containing budesonide when clinically appropriate (e.g., Pulmicort). Cross-reactions may occur with other corticosteroids, including desonide (DesOwen), hydrocortisone (LactiCare), triamcinolone, methylprednisolone (Advantan), prednisolone (Lidomex), and prednicarbate (Dermatop).

Colophonium (colophony, rosin)

Colophonium, also known as colophony or rosin, is an amber-colored resin obtained from pine trees as a residue of turpentine distillation. It is used in products such as crayons, wearable health devices, cosmetics, moisturizers, sunscreens, diapers, sanitary pads, rosin preparations used by musicians and athletes, printer inks, and coated paper products such as copy and photographic paper [33,34]. Medical sources include hydrocolloid dressings, adhesives used with glucose-monitoring devices and insulin pumps, medical tapes, and dental adhesives [15,35]. Colophonium or related resin components may also be encountered in chewing-gum bases and spices such as paprika, nutmeg, and cloves. Industrial uses include varnishes, cleaning products, adhesives, waxes, paints, and soldering materials.

Patients with colophonium allergy should avoid direct contact with sap or sawdust from coniferous trees. Cotton gloves may reduce contact when handling rosin-treated paper, whereas rubber or vinyl gloves may be needed when handling paints, varnishes, pine oil, and related materials. Cross-reactions may occur with wood tar, rosin esters, and substances derived from evergreen species.

Captan

Captan is a fungicide used as an agricultural pesticide. Occupational exposure may occur in farming and fruit production, particularly through contact with treated plants and fruit. Captan may also be present in some soaps and shampoos.

Lanolin (wool alcohol)

Lanolin, which is derived from sheep wool, is used as an emollient and ointment base in many cosmetic and pharmaceutical products. Potential sources include dishwashing detergents, shampoos, soaps, body washes, conditioners, cosmetics, cleansers, nail polish removers, moisturizers, hand creams, masks, and topical medications. Lanolin may also be present in printer inks, lambskin condoms, and industrial polishing products.

Imidazolidinyl urea (Germall 115)

Imidazolidinyl urea (Germall 115) is an antimicrobial preservative used in cosmetics and personal care products. It is a formaldehyde-releasing preservative, as are bronopol, dimethylol dimethyl hydantoin, diazolidinyl urea, and quaternium-15. Products that may contain imidazolidinyl urea include soaps, detergents, shampoos, conditioners, hair sprays, cleansers, exfoliating products, cosmetics, moisturizers, eye creams, perfumes, and deodorants. It has also been reported in ultrasound gels and topical medications [32]. Patients with imidazolidinyl urea allergy should inform their healthcare providers and check ingredient lists before using new products. Previously tolerated products may also trigger reactions if their formulations change.

Quaternium-15

Quaternium-15 is a formaldehyde-releasing preservative used in personal care products such as shampoos, body washes, cosmetics, cleansers, moisturizers, and nail hardeners. It may also be present in disposable masks, wrinkle-resistant fabrics, and electrocardiogram electrode adhesives.

Patients should review ingredient lists and select products that do not contain quaternium-15. Relevant occupational and environmental sources may include industrial oils, plywood, paints, waxes, cigarette smoke, exhaust fumes, and wood smoke.

2-Mercaptobenzothiazole

2-Mercaptobenzothiazole (MBT) is a rubber additive used in a variety of rubber products, including gloves, mats, bands, balloons, erasers, handle grips, electrical cords, earphones, makeup sponges, goggles, swimwear, wetsuits, brassieres, stockings, and shoes. Additional sources include stethoscopes, tokens, dental dams, condoms, elastic diaper edges, and photographic developers [36]. Occupational sources include tires, lubricants, adhesives, masks, tubing, and hoses.

For patients with MBT allergy, both natural and synthetic rubber products should be avoided. If contact cannot be avoided, covering the item with fabric, leather, or plastic may reduce direct skin exposure. Prolonged exposure to MBT may also be associated with sensitization to other rubber chemicals, including thiurams, carbamates, and other mercapto compounds.

Mercapto mix

Mercapto mix is a rubber additive containing N-cyclohexyl-2-benzothiazole sulfenamide, 2,2'-dibenzothiazyl disulfide, and morpholinyl mercaptobenzothiazole. These compounds may be used in the manufacture of rubber products such as gloves, mats, bands, balloons, erasers, handle grips, electrical cords, earphones, makeup sponges, goggles, swimwear, wetsuits, and shoes. Additional sources include stethoscopes, tourniquets, dental dams, and condoms. Occupational exposure may occur through tires, adhesives, masks, tubing, and hoses.

When relevant rubber products must be avoided, vinyl, plastic, leather, wood, or fabric alternatives may be used where appropriate. Prolonged exposure to rubber products may be associated with sensitization to other rubber chemicals, including thiurams, carbamates, and related mercapto compounds.

Clioquinol

Clioquinol is an antimicrobial agent with antibacterial, antifungal, and antiprotozoal activity. It has been used in medicated dressings and in topical and intestinal anti-infective labels before using topical creams, ointments, or vaginal preparations.

Occupational contact allergens

Hairdressers

Hairdressers with metal allergies should minimize direct contact with metallic tools such as scissors, combs, curling irons, hairpins, and hair clips [37]. Nickel release from metallic tools may be increased by exposure to chemicals used in salons. Latex gloves may permit more rapid penetration of allergens in permanent-wave solutions; therefore, vinyl or nitrile gloves may be preferable [48]. However, individuals allergic to rubber accelerators such as thiurams should exercise caution with rubber bands and may need to avoid latex or nitrile gloves in favor of vinyl gloves. Those with allergies to fragrances or preservatives, including parabens, formaldehyde, and MCI/MI, should avoid hair products containing the relevant allergens. Individuals with paraben allergy should also avoid paraben-containing waxes. Those allergic to PPD should avoid PPD-containing hair dyes and should be aware of potential exposure to cross-reacting dyes, including those in some surgical marking pens. Bleaching and permanent-wave products may also cause contact reactions [48].

Healthcare workers

Healthcare workers allergic to rubber accelerators such as thiurams should avoid rubber gloves (e.g., latex, nitrile, and neoprene) and use polyethylene or vinyl alternatives [49]. Those allergic to preservatives such as quaternium-15 should check hand sanitizers, soaps, and hand creams for relevant allergens. Healthcare workers with rubber accelerator allergy should avoid rubber-containing mask straps when clinically relevant. Those with formaldehyde allergy should consider potential exposure from disposable surgical masks, whereas individuals with nickel or cobalt allergy should consider potential metal exposure from N95 respirators. Patients with colophonium allergy should avoid relevant plasters, adhesive bandages, and hydrocolloid dressings. Individuals with thimerosal allergy should inform their healthcare providers before vaccination so that the formulation can be assessed without unnecessarily delaying immunization. Those allergic to PTBP should consider potential exposure from electrocardiogram electrodes and bispectral index sensors [48].

Dentists and dental hygienists

Dentists and dental hygienists with allergy to rubber accelerators such as thiurams should avoid rubber gloves (e.g., latex, nitrile, and neoprene) and use polyethylene or vinyl alternatives. Those with allergies to metals such as nickel, cobalt, or chromium should minimize direct exposure to metal-containing dental materials, including bridges, crowns, and dentures, as some allergens may penetrate gloves within minutes. Occupational allergic reactions may also occur in association with local anesthetic preparations, impression materials, mercury amalgam, dental cement, essential oils, and other substances. Because acrylic resins may cause airborne exposure, adequate ventilation should be maintained when these materials are handled. Exposure to formaldehyde during instrument sterilization should also be minimized.

Cooks

Cooks with metal allergies should minimize direct contact with metallic cookware and utensils when these items contain the relevant allergen. Individuals allergic to nickel, cobalt, or chromium should also consider the potential for exposure when handling ingredients such as legumes, whole grains, cabbage, tea, and cocoa. Those allergic to rubber accelerators such as thiurams should use gloves without the relevant accelerators; vinyl gloves may be an appropriate alternative to some latex or nitrile gloves. Individuals allergic to Balsam of Peru or fragrance mixes may need to avoid relevant flavorings and spices, including vanilla extract and cinnamon. Certain preservatives, including benzoin, have also been reported to cause airborne contact urticaria without direct skin contact.

Guidance on selecting allergen-free alternatives

Patch testing

Repeated open application tests may help assess suspected products in patients with ACD.

Product labeling

Consider products labeled "hypoallergenic," "fragrance-free," or "sensitive skin" to reduce the risk of allergic reactions.

Ingredient awareness

Patients should become familiar with their allergens and alternative ingredient names to reduce inadvertent exposure.

Natural alternatives

Natural and organic products, specifically those containing minimal additives and preservatives, may be considered to lower

the risk of allergic reactions.

Healthcare consultation

Dermatologists or allergists can provide individualized guidance regarding allergen avoidance and treatment.

Discussion

Interpretation

This review updates information on the KSS by incorporating emerging or newly recognized sources of allergen exposure, including electronic devices, newer cosmetic products, and personal protective equipment. Because the existing patient information has not been substantially revised for more than 2 decades, these updates may help align allergen-avoidance guidance with contemporary exposures and may also inform future evaluation of changing exposure patterns in ACD. Interpretation of patch test results should distinguish among patch test positivity, clinical relevance, and current relevance. A positive reaction generally indicates sensitization to the tested allergen; clinical relevance considers whether that sensitization is related to a patient's dermatitis, whereas current relevance indicates whether the allergen contributes to the present episode. Because some allergens may produce positive reactions that have only historical or limited clinical relevance, avoidance recommendations should be based on the clinical significance of the reaction rather than patch test positivity alone.

Limitations

First, the narrative review design and restriction to English-language literature may have introduced selection bias and excluded relevant regional evidence. Second, empirical epidemiological data regarding the prevalence and clinical relevance of these emerging sources specifically in the Korean population remain limited.

Implications

Dermatologists can use these updated education sheets to support patient allergen avoidance. Furthermore, this review highlights the need for a formal revision of the KSS by Korean dermatological societies and for future prospective cohort studies to evaluate sensitization rates to these emerging environmental exposures.

Conclusion

Providing patients with comprehensive and accessible information is essential for managing ACD. Understanding specific allergens and potential cross-reactors may help patients identify clinically relevant exposures and reduce inadvertent contact and subsequent reactions.

Ultimately, the goal is to promote a proactive approach to allergen management. Continued education and technological tools may help patients make more informed decisions about allergen avoidance. Strategies such as allergy passes, smartphone applications, and legal protections may also be beneficial in supporting allergen avoidance [1].

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Authors' contribution

Conceptualization: HYC. Data curation: JC. Methodology/formal analysis/validation: JC, HYC. Project administration: HYC. Writing–original draft: JC. Writing–review & editing: JC, HYC.

Conflict of interest

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Supplementary materials

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Supplement 1. Korean Standard Series allergen sheets in Korean.

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인공지능 시대의 영문 편집: 인식적 무결성 확보하기

Language editing in the artificial intelligence era: achieving epistemic integrity—an expanded Korean translation

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Large language models (LLMs) are increasingly used to write and edit scientific manuscripts; however, their fluency can obscure mismatches between linguistic claim strength and evidential support. This tutorial examines such mismatches through the lens of epistemic integrity, defined as accurate alignment of scientific statements with the quality, strength, and scope of the underlying evidence. It presents sentence-level epistemic markers that require careful human judgment, including reporting verbs, hedges, tense choices, evaluative adjectives and adverbs, and local scope markers. Inappropriate modification of these features can overstate or understate certainty, strengthen or weaken a claim beyond what the evidence warrants, or distort an author's intended emphasis. The tutorial also addresses discourse-level issues, including the need to clearly distinguish between results and interpretation, shifts in certainty across manuscript sections, consistency in scope limitations, and cumulative changes in evaluative tone. Because LLMs cannot independently assess study design, methodological limitations, disciplinary conventions, or evidential sufficiency, polished revisions may introduce epistemic miscalibration even when they are grammatically correct. Editors should therefore evaluate not only local wording but also the consistency of claims across the manuscript. Human editorial expertise remains essential for preserving rhetorical coherence, evidential accuracy, and scientific integrity in artificial intelligence–assisted academic writing, alongside attention to grammar, style, clarity, and readability.

Keywords: Large language model; Language editing; Epistemic integrity; Epistemic calibration; Epistemic markers

서론

배경

연구 진실성(research integrity)은 흔히 연구의 윤리적 수행과 소통에 관한 문제로 이해된다. 즉 연구자는 날조, 변조, 표절과 같은 연구부정행위를 피해야 한다. 그러나 이러한 도덕적 의무만으로 연구 진실성의 개념이 모두 설명되는 것은 아니다. 연구 진실성에는 인식적 차원(epistemic dimension)도 존재한다. 과학적 주장은 이를 뒷받침하는 근거의 질, 강도 및 범위에 관하여 독자를 오도해서는 안 된다. De Winter와 Kosolosky [1]는 이러한 차원을 '인식적 무결성(epistemic integrity)'으로 개념화하고, 이를 연구 진실성의 도덕적 측면과 구분하여 과학적 실천을 통해 생성되는 진술의 신뢰성과 비기만성(non-deceptiveness)에 연결하였다. 따라서 인식적 무결성은 과학적 진술이 이를 뒷받침하는 근거가 허용하는 수준을 얼마나 충실하게 반영하는가와 관련된다.

과학적 주장은 언어를 통해 독자에게 전달되며, 이는 주로 문자언어의 형태를 취하지만 반드시 이에 국한되지는 않는다. 따라서 인식적 무결성은 연구자가 무엇을 주장하는가뿐만 아니라 그 주장

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을 어떻게 표현하는가와도 밀접하게 관련된다. 연구자는 다양한 언어 자원을 활용하여 자신의 입장(stance)을 구성하고, 연구결과의 인식적 지위와 근거가 제공하는 뒷받침 수준에 맞추어 주장의 확실성, 범위 및 해석의 수준을 조율한다[2-4].

경험 많은 편집인에게 언어와 근거 간의 조율(calibration)은 새로운 문제가 아니다. 편집인들은 오래전부터 언어적 선택이 근거가 정당화하는 수준의 확실성, 범위 및 해석을 적절히 반영하는지를 평가해 왔다. 그러나 연구설계, 방법론적 한계 또는 기타 관련 근거를 충분히 고려하지 않은 상태에서도 유창한 텍스트를 생성할 수 있는 대규모 언어 모델(large language models, LLMs)이 널리 활용되면서 이러한 판단의 중요성이 더욱 커졌다[5]. LLM이 생성하거나 수정한 문장은 문법적으로 정확하고 자연스러워 보이더라도, 해당 연구의 근거가 정당화하는 '인식적 수준'을 적절히 반영하지 못할 수 있다. 최근 연구들은 LLM이 자신의 응답 정확성에 관한 불확실성을 언어적으로 얼마나 적절히 표현하는지에도 의문을 제기하고 있다[6-8]. 모델이 언어로 표현하는 확실성은 실제 응답의 정확성이나 모델 내부에서 추정되는 불확실성과 일치하지 않을 수 있으며, 일부 연구에서는 이러한 과잉 확신의 정도가 상당한 수준에 이를 수 있음이 보고되었다[9]. 이러한 연구가 학술논문의 근거-주장 관계를 직접 다루는 것은 아니지만, LLM이 생성하는 확신의 언어를 근거에 대한 신뢰할 만한 평가로 간주해서는 안 된다는 점을 시사한다. 학술 글쓰기와 편집의 맥락에서는 이러한 불일치가 근거가 실제로 정당화하는 수준과 언어적으로 표현된 주장의 확실성, 범위 또는 해석 수준 사이의 간극, 즉 '인식적 오조율(epistemic miscalibration)'로 나타날 수 있다.

목적

본 튜토리얼은 인식적 표지(epistemic markers)로 기능하는 언어적 요소들을 살펴보고, LLM이 이러한 요소들을 부적절하게 선택하거나 수정할 때 문장 및 담화 수준에서 인식적 오조율(epistemic miscalibration)이 어떻게 발생할 수 있는지를 설명한다. 본고의 목적은 첫째, 언어적 선택이 주장의 확실성, 범위 및 해석 수준을 어떻게 조절하는지에 대해 저자와 학술지 편집인의 주의를 환기하고, 둘째, 적절한 인식적 조율을 위해서는 언어와 연구 근거, 그리고 학문 분야별 관습을 종합적으로 고려하는 인간의 해석과 판단이 필요함을 강조하며, 셋째, LLM의 도움으로 다듬어진 언어적 유창성이 근거와 주장 사이의 인식적 오조율을 가릴 수 있음을 보여주는 데 있다.

문장 수준의 인식적 표지

저자와 심사자는 인식적 표지(epistemic markers)를 개별적이고 국소적인 언어 선택으로 인식할 수 있다. 그러나 언어 교정의 관점에서 문장 수준의 수정은 문법 오류를 바로잡거나 문체를 다듬는 데 그치지 않고, 언어적으로 표현된 확실성, 범위 및 해석의 수준이 연구 근거에 적절히 부합하는지를 판단하는 작업까지 포함한다. LLM은 이러한 인식적 차원을 근거에 맞게 조율하지 못하고 확실성이나 불확실성을 부적절하게 표현할 수 있다. 또한 인간 피드백에 기반한 학습과정에서는 사용자가 불확실성을 드러내는 응답보다 단정적이고 확신에 찬 응답을 선호하는 경향이 보고되었으며[10,11], 이러한 선호는 LLM이 생성하는 언어의 확실성에도 영향을 미칠 가능성이 있다. 그 결과 필요한 헤지(hedges)가 약화되거나 삭제되고, 근거가 충분히 뒷받침하지 않는 수준의 단정적인 표현이 생성될 수 있다. 이러한 경향은 사용자의 기대나 관점에 지나치게 부응하려는 LLM의 성향과 결합하여[12], 근거에 맞게 불확실성과 주장의 범위를 조율해야 하는 과학적 글쓰기에서 인식적 무결성을 훼손할 수 있다.

본 튜토리얼에서는 분석과 설명의 편의를 위해 인식적 표지를 동사, 헤지 표현, 시제, 평가적 수식어, 범위 표지의 다섯 가지 유형으로 구분하여 살펴본다. 이러한 언어적 요소에 대한 LLM의 수정은 개별적으로는 미미해 보일 수 있지만, 궁극적으로는 주장의 확실성, 적용범위, 근거에 대한 평가 및 해석 수준을 변화시킬 수 있다.

동사의 선택

동사는 미묘한 의미 차이를 지니며, 저자가 연구결과나 해석을 어느 정도의 확실성으로 제시하는지를 드러내는 중요한 언어적 자원이다. 따라서 동사는 연구설계, 결과의 일관성, 방법론적 한계, 그리고 학문 분야별 관습을 고려하여 선택되어야 한다. 그러나 LLM은 표본크기, 실험연구와 관찰연구의 구분, 통제되지 않은 변수 등 적절한 동사 선택에 필요한 연구 맥락을 충분히 고려하지 못할 수 있다. 또한 사용자의 기대나 관점에 지나치게 부응하는 아첨적 동조(sycophancy) 경향은 결과나 해석을 보다 확신에 찬 언어로 표현하는 방향으로 작용할 가능성이 있다[12]. 이 경우 근거가 정당화하는 수준보다 강한 동사가 선택되어 주장의 확실성이 과도하게 높아질 수 있다. 다음은 이러한 문제를 잘 보여주는 단순화된 예시이다.

(1) The results demonstrate (vs. indicate or suggest) an association between X and Y.
(2) The results suggest (vs. demonstrate or indicate) a causal effect of X on Y.

"Demonstrate," "indicate," 그리고 "suggest"는 일반적으로 서로 다른 정도의 인식적 확신을 전달한다. "Demonstrate"는 뒤따르는 주장이 근거에 의해 비교적 강하게 뒷받침되고 있음을 나타내는 반면, "suggest"는 보다 제한적이거나 잠정적인 해석을 제시하는 데 흔히 사용된다. "Indicate"는 문맥에 따라 그 사이의 의미를 나타낼 수 있다. 동사 선택의 적절성은 동사의 강도만으로 판단할 수 없으며, 동사가 결합하는 명제의 성격과 이를 뒷받침하는 연구 근거를 함께 고려해야 한다. 예를 들어, 충분한 방법론적 근거를 갖춘 대규모 무작위 대조시험(randomized controlled trial)에서 특정 효과가 일관되게 확인되었다면 "demonstrate"와 같은 비교적 강한 동사의 사용이 정당화될 수 있다. 반면, 제한된 표본에서 탐색적으

로 관찰된 결과라면 "observe"나 "suggest"와 같은 표현이 더 적절할 수 있다. 그러나 "suggest"와 같이 비교적 신중한 동사를 사용하더라도, 그 뒤에 근거가 뒷받침하지 못하는 인과적 주장이 이어진다면 전체 표현은 여전히 부적절할 수 있다.

주의해야 할 것은 이러한 인식적 함의는 목적어와 연구 맥락에 따라서 달라지기도 한다. 예를 들어, 연구자가 제한된 표본에서 얻은 결과를 신중하게 제시하기 위해 "We observed a trend toward improved performance"라고 썼다고 가정했을 때, 이를 LLM이 "The analysis confirmed a trend toward improved performance"로 수정하면 문장이 단순히 더 단정적으로 들리는 데 그치지 않고, 관찰된 결과에 부여되는 인식적 확실성이 높아질 수 있다. 따라서 편집인은 연구설계, 방법론적 한계, 연구범위와 결과의 일관성 등을 고려하여 해당 주장을 근거가 어느 정도까지 뒷받침하는지 판단하고, 이러한 판단이 동사 선택에 적절히 반영되어 있는지를 검토해야 한다. 특히 LLM을 활용한 수정과정에서는 동사의 인식적 강도가 근거 없이 높아지거나 낮아지지 않았는지 확인할 필요가 있다. 언어적으로 매끄러운 문장일수록 이러한 근거-주장 간의 불일치가 쉽게 드러나지 않을 수 있기 때문이다.

헤지 표현

일반적인 헤지 표현(hedges)에는 조동사(may, might, could), 부사(possibly, potentially, perhaps), 동사(suggest, appear, seem) 등이 포함된다. 헤지는 단순히 신중한 태도를 나타내는 언어적 장치가 아니라, 근거가 허용하는 수준에 맞추어 주장의 확실성을 조절하고 불확실성의 정도를 드러내는 기능을 한다[2]. 헤지를 지나치게 사용하면 주장이 근거에 비해 불필요하게 약화될 수 있고, 반대로 필요한 헤지를 사용하지 않으면 주장이 지나치게 단정적으로 제시될 수 있다. 다음은 이러한 문제를 보여주는 예시이다.

(1) This treatment improves insulin sensitivity.
(2) This treatment may improve insulin sensitivity.
(3) This treatment might potentially improve insulin sensitivity.

예를 들어, 표본이 작고 결과의 불확실성이 상당한 경우라면 문장 (2)가 근거에 보다 적절하게 조율된 표현일 수 있다. 그러나 LLM은 헤지를 삭제하여 문장 (1)과 같이 지나치게 단정적인 표현으로 바꾸거나, 반대로 문장 (3)처럼 의미가 중복되는 헤지를 덧붙여 주장을 필요 이상으로 약화시킬 수 있다.

문제는 헤지가 때때로 근거에 대한 인식적 판단의 결과라기보다 신중하거나 정중한 문체를 만드는 장치로 취급될 수 있다는 점이다. 예를 들어, "The results may prove that the method is effective"에서 "may"는 불확실성을 나타내지만, "prove"는 뒤따르는 주장에 매우 높은 수준의 확실성을 부여한다. 이처럼 서로 다른 수준의 인식적 확신을 나타내는 표현이 한 문장 안에 결합되면, 저자가 해당 주장에 어느 정도의 확신을 부여하는지가 불명확해질 수 있다. 과학적 글쓰기에서 헤지는 신중하고 객관적인 문체를 형성하는 데 기여할 수 있지만, 핵심은 주장을 약하게 표현하는 데 있는 것이 아니라 근거가 허용하는 수준의 불확실성을 정확하게 표현하는 데 있다. 따라서 인식적 조율(epistemic calibration)은 헤지의 유무나 빈도 자체가 아니라, 해당 주장에 부여된 불확실성의 정도가 연구 근거에 의해 정당화되는가에 달려 있다. LLM을 활용한 수정에서는 이러한 관계가 충분히 고려되지 않은 채 헤지가 추가되거나 삭제될 수 있으므로, 편집인은 헤지가 문체적 신중함을 위한 장식이 아니라 근거와 주장 사이의 관계를 정확하게 조율하고 있는지를 검토해야 한다.

시제 선택

학술 글쓰기에서 현재시제는 일반적으로 보편적 사실이나 현재 받아들여지는 지식을 제시하는 데 사용되며, 과거시제는 방법이나 결과와 같이 완료된 연구를 보고하는 데 사용된다. 현재완료는 과거의 연구나 사건을 현재의 논의와 연결할 때 주로 사용된다. 그러나 시제 선택은 단순히 사건의 시간적 위치를 나타내는 데 그치지 않고, 연구결과를 어느 범위까지 일반화하여 제시할 것인지와 관련된다는 점에서 인식적 기능도 수행한다. 예를 들어, "A phenomenon was observed"는 특정 연구와 조건에서 관찰된 결과를 보고하는 반면, "A phenomenon is observed"는 해당 현상을 보다 일반적인 경험적 패턴으로 제시하고 있다. 이처럼 특정 맥락에서 과거시제는 결과를 해당 연구의 관찰범위에 한정하는 효과를 갖는 반면, 현재시제는 그 결과를 보다 일반화된 지식이나 해석으로 제시하여 주장의 적용범위를 넓힐 수 있다. 따라서 과거시제에서 현재시제로의 변화는 단순한 문법적 수정이 아니라 연구결과가 어느 범위까지 적용되는지에 대한 해석을 변화시킬 수 있다.

시제 사용에 관한 관습은 학문 분야와 논문의 수사적 맥락에 따라 달라질 수 있으므로, 편집인은 해당 분야의 관습과 문장의 기능을 함께 고려하여 판단해야 한다. 문제는 LLM이 이러한 맥락을 충분히 고려하지 않은 채 문법적 또는 문체적 일관성을 위해 시제를 변경할 때 발생할 수 있다[13]. 과거시제를 현재시제로 바꾸면 연구 특이적인 결과가 지나치게 일반화될 수 있고, 반대로 현재시제를 과거시제로 바꾸면 저자가 의도한 일반화된 해석이나 현재적 타당성이 약화될 수 있다. 요컨대 시제의 불일치는 반드시 바로잡아야 할 문법적 오류가 아니다. 표면적으로 불일치해 보이는 시제의 변화가 실제로는 주장의 범위나 저자의 인식적 입장의 차이를 나타낼 수 있기 때문이다. 따라서 영문 교정자는 시제를 기계적으로 통일하기보다, 각 시제가 수행하는 수사적 · 인식적 기능을 파악하고 연구 근거가 허용하는 범위 안에서 그 선택의 타당성을 검토해야 한다.

평가적 수식어

연구자는 "clear/clearly, substantial/substantially, strong/strongly, compelling"과 같은 평가적 형용사와 부사를 사용하여 연구결과나 근거의 특정 측면을 강조한다. 이러한 수식어는 주장의 확실성, 효과의 크기, 근거의 강도 등 서로 다른 측면을 선택적으로 부각할 수 있다. 예를 들어 "The treatment clearly reduced postoperative pain"에서 "clearly"는 결과에 대한 높은 확신을 나타내

고, "The drug substantially improved glycemic control"에서 "substantially"는 효과의 크기를 강조한다. 또한 "The findings provide compelling evidence that the intervention improves glycemic control"에서 "compelling"은 제시된 근거를 강력한 것으로 평가한다. 이처럼 평가적 수식어는 동일한 연구결과에서도 확실성, 효과의 크기, 근거의 강도 등 서로 다른 측면을 선택적으로 부각한다.

편집하는 과정에서 LLM이 연구 근거와 맥락을 충분히 고려하지 않은 채 이러한 수식어를 삽입하거나 강화하게 되면 문제가 발생할 수 있다. 예를 들어, LLM이 "The treatment reduced postoperative pain"을 단지 더 명확하거나 설득력 있게 들리도록 하기 위해 "The treatment clearly reduced postoperative pain"으로 수정할 수 있다. 그러나 연구 근거가 "clearly"가 나타내는 높은 수준의 확신을 정당화하지 않는다면, 이러한 수정은 단순한 문체 개선이 아니라 결과에 부여되는 확실성을 부적절하게 높이는 변화가 된다. 평가적 수식어는 단순히 주장을 더 강하게 만드는 것이 아니라, 연구결과와 근거의 서로 다른 측면에 대한 저자의 평가를 언어적으로 드러내는 것이다. 따라서 영문 교정자는 평가적 수식어를 단순한 문체적 강조 장치로 보지 않고, 각 수식어가 결과나 근거의 어떤 측면을 부각하며 그러한 평가가 연구 근거에 의해 정당화되는지를 검토해야 한다.

국소적 범위 표지

국소적 범위 표지(local scope markers)는 문장 수준에서 주장이 적용되는 범위를 제한한다. 예로는 "in this study, under the tested conditions, in high-risk patients, in this cohort" 등이 있다. 가령 "The method was effective under the tested conditions,"라는 표현은 연구결과가 특정 맥락에 한정된다는 점을 명시한다. LLM은 적절한 범위 표지를 삭제하거나 필요한 범위 표지를 반영하지 않음으로써 근거가 허용하는 수준을 넘어 주장의 적용범위를 부주의하게 확대하고, 의도하지 않은 과잉 일반화를 초래할 수 있다. 영문 교정자는 필요한 경우, 범위 표지를 복원하거나 추가하여 주장이 근거가 허용하는 경계 안에 머물도록 해야 한다. 범위 표지는 모집단, 연구환경, 중재, 측정조건, 시간범위를 명확히 하며, 이를 삭제하면 특정 조건에 한정된 결과가 보다 일반적인 주장으로 미묘하게 확대될 수 있다.

본 섹션에서는 인간 편집인의 판단이 필요한 인식적 표지를 다섯 가지 유형으로 구분하여 살펴보았다. 그러나 이러한 구분은 분석을 위한 것이며, 실제 학술 글쓰기에서 각 표지가 독립적으로 기능하지 않고 서로 결합하여 주장의 인식적 성격을 형성한다. 따라서 실제 편집과정에서는 개별 표지를 분리하여 평가하기보다 이들의 상호작용과 복합적 효과를 함께 고려해야 한다. 특히 LLM을 활용한 논문에서는 동사, 헤지, 시제, 평가적 수식어 등 여러 언어적 장치가 동시에 변경되면서 저자가 의도한 인식적 입장이 과장되거나 축소될 수 있다. 따라서 영문 교정자는 개별 표현의 적절성뿐 아니라 이들이 결합하여 형성하는 전체적인 인식적 입장(epistemic stance)이 근거의 강도와 범위에 부합하는지를 판단하고, 연구 주장의 정확성과 인식적 무결성이 유지되도록 해야 한다.

담화 수준의 인식적 표지

LLM이 생성한 텍스트를 문장 수준에서 검토하다 보면 동사의 미세한 강화, 겉보기에는 사소한 헤지 삭제, 미묘한 시제 변화 등이 발견될 수 있다. 영문 교정자는 연구 근거에 비해 주장을 지나치게 강화하거나 약화시키지 않는지 검토하고, 필요한 경우 근거에 맞게 다시 조정하곤 한다 각각의 변화는 개별적으로는 미미해 보일 수 있지만, 논문 전체에 걸쳐 누적되면 저자의 인식적 입장(epistemic stance)에 상당한 변화를 가져올 수 있다. 따라서 담화 수준에서는 개별 문장의 적절성뿐만 아니라, 저자가 연구결과에 대해 어느 정도의 확신과 신중성을 나타내며 이러한 인식적 입장이 논문 전체에서 어떻게 형성되고 변화하는지를 함께 살펴보아야 한다. 본 섹션에서는 개별 인식적 표지를 넘어 논문 전체에서 형성되는 인식적 입장에 주목하고, 특히 섹션 간 입장 표류(stance drift)를 식별하고 조정하기 위해 편집인은 어떠한 판단이 필요한지 살펴본다.

결과와 해석의 경계

담화 수준에서 중요한 경계 중 하나는 연구결과의 보고와 그 의미에 대한 해석을 구분하는 것이다. 일반적으로 결과(Results) 섹션에서는 관찰되거나 분석된 결과를 중심으로 보고하고, 고찰(Discussion) 섹션에서는 그 결과를 해석하고 기존 연구와의 관계, 함의 및 의의를 논의한다. 이러한 구분의 정도는 학문 분야와 학술지의 관행에 따라 달라질 수 있다. 그러나 LLM을 활용한 수정은 이러한 수사적 인식적 경계를 흐릴 수 있다. 예를 들어, 결과 섹션에 다음과 같은 문장이 있다고 가정했을 때, "The model achieved higher accuracy than the baseline, implying its potential clinical applicability," 이 문장은 문법적으로는 문제가 없지만, "implying its potential clinical applicability"는 관찰된 결과를 보고하는 데 그치지 않고 그 결과로부터 임상적 함의를 도출하는 해석을 덧붙인다. 즉 단순한 경험적 결과의 보고에서 그 결과의 의미에 대한 해석으로 담화 기능이 이동하게 된 것이다. LLM은 문장 간 연결을 매끄럽게 하거나 결과의 의미를 보다 명확하게 제시하는 과정에서 이러한 해석적 표현을 추가할 수 있다. 그러나 그 결과, 관찰된 사실과 그 사실로부터 도출된 해석 사이의 경계가 불분명해지고, 해석이 마치 연구결과 자체의 일부인 것처럼 제시될 수 있다. 따라서 영문 교정자는 해당 표현이 그 섹션의 수사적 기능에 적절한지를 판단하고, 필요한 경우 이를 고찰 섹션으로 옮기거나 결과 보고에 적합한 형태로 조정해야 한다.

섹션 간 인식적 확실성

논증이 전개됨에 따라 주장의 확실성이나 해석의 수준이 달라질 수 있지만, 이러한 변화는 자의적이어서는 안 되며 연구 근거와 논증의 전개에 의해 정당화되어야 한다. 따라서 영문 교정자는 개별 문장의 적절성뿐 아니라 논문 전체에서 인식적 어조(epistemic tone)가 일관되게 유지되는지를 검토해야 한다. LLM으로 인해 발

생할 수 있는 입장 표류(stance drift)의 한 형태는 논문의 후반부로 갈수록 별다른 근거 없이 주장이 강화되는 것이다.

결과 섹션의 "A positive association was observed between X and Y"와 고찰 섹션의 "These findings demonstrate that X plays a critical role in Y"를 비교해 볼 때, 각 문장을 개별적으로 보면 뚜렷한 언어적 문제는 없어 보인다. 그러나 두 문장을 논문 전체의 흐름에서 비교하면, 결과 섹션에서 보고된 연관성이 고찰 섹션에서는 X의 역할에 대한 보다 강한 해석으로 전환되고 있음을 알 수 있다. 이는 단순한 표현상의 변화가 아니라 주장의 성격과 그 주장에 부여되는 확실성이 함께 변화한 사례이다. "was observed"는 해당 연구에서 X와 Y 사이의 연관성이 관찰되었음을 보고하는 반면, "demonstrate"는 뒤따르는 해석이 근거에 의해 상당한 수준으로 확립되었음을 시사한다. 또한 "X plays a critical role in Y"는 단순한 연관성을 넘어 X의 인과적 또는 기능적 역할에 대한 해석을 제시한다.

고찰 섹션에서는 결과를 해석하고 그 의미를 논의하기 때문에 결과 섹션보다 더 강한 언어를 사용하는 것이 자연스럽다고 여겨질 수 있다. 그러나 새로운 근거나 방법론적 정당화가 없다면, 고찰 섹션이라는 이유만으로 관찰된 연관성을 더 강한 해석으로 전환하거나 이에 대한 확실성을 높여서는 안 된다. 편집인은 이러한 섹션 간 변화를 추적하여 주장의 성격과 이에 부여되는 확실성의 변화가 연구 근거와 논증의 전개에 의해 정당화되는지를 확인하고, 그렇지 않은 경우 적절한 수준으로 다시 조율해야 한다.

담화 수준의 과잉 일반화

과잉 일반화(overgeneralization)는 한 문장 안에서 발생할 수도 있지만, 논문이 전개되는 과정에서 범위를 제한하는 표현이 점차 약화되거나 삭제되면서 누적적으로 나타나기도 한다. 다음은 과잉 일반화의 예시이다.

(1) "In this cohort, the intervention improved outcomes."
(2) "The intervention improved outcomes."
(3) "The intervention was effective."

(1)에서 (2)로 이동하면서 연구대상 모집단을 한정하는 "in this cohort"가 삭제되고, (2)에서 (3)으로 이동하면서 구체적으로 관찰된 결과가 중재의 전반적인 효과성에 대한 보다 포괄적인 평가로 전환된다. 각 단계의 변화는 개별적으로는 미미해 보일 수 있지만, 이러한 변화가 논문 전반에 걸쳐 누적되면 주장의 적용범위가 근거가 직접 뒷받침하는 범위를 넘어 점차 확대될 수 있다.

LLM은 간결성이나 문체적 일관성을 높이는 과정에서 범위 표지를 삭제하거나 구체적인 결과를 보다 일반적인 표현으로 바꿀 수 있다. 따라서 영문 교정자는 개별 문장뿐 아니라 논문 전체에서 주장의 범위가 어떻게 변화하는지를 추적하고, 연구설계와 연구대상 모집단 등을 고려하면서, 그 범위가 연구 근거가 실제로 뒷받침하는 수준을 벗어나지 않는지 검토해야 한다.

논문 전반의 인식적 · 평가적 어조

문장 수준에서는 헤지나 평가적 수식어와 같은 언어적 장치가 개별 주장의 확실성이나 평가방식을 조절하지만, 담화 수준에서는 이러한 표현의 누적적 사용이 논문 전체의 인식적 · 평가적 어조를 형성한다. 예를 들어, LLM이 "may"나 "appears to"와 같은 헤지를 반복적으로 삭제하면, 각각의 수정은 사소해 보이더라도 논문 전체는 원래보다 지나치게 단정적인 어조를 띨 수 있다. 마찬가지로 한계나 문제점을 기술하는 과정에서 "serious limitation"이나 "critical issue"와 같은 표현이 반복되면 논문 전체가 필요 이상으로 부정적이거나 방어적인 어조를 띨 수 있다. 반대로 긍정적 평가 표현이 반복되면 연구의 의의가 과도하게 강조되어 과장된 어조가 형성될 수 있다. 따라서 영문 교정자는 개별 표현의 빈도 자체보다는 이러한 표현이 논문의 어느 부분에서 어떠한 기능으로 사용되는지 살펴보고, 그 결과 형성되는 인식적 · 평가적 어조가 연구 근거와 각 섹션의 수사적 기능에 비추어 적절한지를 판단해야 한다.

편집인을 위한 시사점

본 튜토리얼은 LLM이 생성하거나 수정한 텍스트의 언어적 유창성이 인식적 무결성(epistemic integrity)과 반드시 일치하지 않으며, 이로 인해 문장 및 담화 수준에서 인식적 오조율(epistemic miscalibration)이 발생할 수 있음을 보여주었다. 인식적 무결성을 유지하려면 연구 주장이 근거가 뒷받침하는 확실성, 범위 및 해석의 수준을 넘어서는 안 되며, 이러한 인식적 특성은 동사, 헤지, 시제, 평가적 수식어, 범위 표지와 같은 다양한 언어적 장치를 통해 부분적으로 표현된다. LLM을 활용한 수정과정에서는 이러한 언어적 장치가 근거와의 관계를 충분히 고려하지 않은 채 변경되면서 주장이 과도하게 강화되거나 약화되기도 한다. 또한 서로 다른 수준의 확실성이나 범위가 획일화될 수도 있다. 따라서 인공지능(artificial intelligence) 시대의 영문 교정자는 문법과 문체를 점검하는 데 그치지 않고, 이러한 국소적 인식적 표지가 연구 근거에 부합하도록 적절히 조율되어 있는지를 검토해야 한다.

담화 수준에서도 인간의 판단은 필수적이다. 논문의 인식적 입장은 모든 섹션에서 동일하게 유지되어야 하는 것이 아니라, 연구 근거와 각 섹션의 수사적 기능에 따라 적절하게 변화하고 전개되어야 한다. 그러나 LLM이 생성한 텍스트의 높은 유창성은 섹션 간 주장 범위나 확실성, 해석 수준의 미묘한 변화를 놓치게 만들기도 하기 때문에 입장 표류(stance drift)를 발견하기 어려운 경우도 있다. 따라서 편집인은 먼저 논문의 핵심 주장을 식별하고, 이들이 결과, 고찰, 결론을 거치면서 어떻게 변화하는지를 추적해야 한다. 특히 이러한 변화가 연구 근거에 의해 정당화되는지를 검토함으로써, 논문 전체에서 근거와 주장 사이의 적절한 조율이 유지되도록 해야 한다.

LLM이 학술 글쓰기와 편집과정에 점점 더 깊이 통합됨에 따라 인간의 판단이 불필요해지는 것이 아니라, 오히려 편집 및 검토과정에서 요구되는 판단의 범위가 확대될 수 있다. 문법, 문체, 명료성, 가독성에 대한 기존의 점검에 더해, 언어적 선택이 연구 근거와 주

장의 관계를 왜곡하지 않는지를 검토하는 인식적 감독(epistemic oversight)이 요구되기 때문이다. 따라서 인간 편집인의 전문적 판단은 여전히 필수적이며, 특히 미세한 언어적 변화가 연구 결과에 부여되는 확실성, 적용범위 및 해석 수준을 실질적으로 변화시킬 수 있기 때문에, 학술 출판 맥락에서 편집인의 역할은 더욱 중요하다.

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Authors' contribution

Conceptualization: YW. Methodology/formal analysis/validation: YW, AD. Project administration: YW. Writing–original draft: YW. Writing–review & editing: YW, AD.

Conflict of interest

Andrew Dombrowski serves as the English editor for this journal, but was not involved in the peer review or decision-making process of this article. No other potential conflict of interest relevant to this article was reported.

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Not applicable.

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The burden of neck pain across US states, 1990–2021: a systematic analysis of Global Burden of Disease Study 2021 data

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Purpose: Neck pain is a leading musculoskeletal cause of disability in the United States. This study aimed to assess temporal, geographic, and demographic disparities in its burden across US states from 1990 to 2021.

Methods: Global Burden of Disease 2021 data for all 50 US states and the District of Columbia were analyzed for 1990–2021. Counts and age-standardized rates per 100,000 population for prevalence, incidence, and years lived with disability (YLD) were compared by region, state, sex, age group, and sociodemographic index (SDI) level.

Results: In 2021, neck pain accounted for 9,430,000 (95% uncertainty interval [UI], 7,400,000–11,590,000) prevalent cases, 1,900,000 (95% UI, 1,490,000–2,320,000) incident cases, and 920,000 (95% UI, 620,000–1,300,000) YLD, increases of 41.17%, 37.44%, and 38.72%, respectively, from 1990. Although age-standardized incidence increased globally by 1.18% (0.07%–2.39%) over 1990–2021, the United States had small declines in age-standardized incidence (−0.11%; 95% UI, −0.18% to −0.06%), prevalence (−0.20%; 95% UI, −0.32% to −0.10%), and YLD (−1.12%; 95% UI, −2.02% to −0.22%). Neck pain rates were highest in the District of Columbia, Georgia, and Delaware and lowest in North Carolina, Alaska, and Wyoming. The burden peaked at ages 40–49 years and was higher in females. Age-standardized YLD rates for neck pain were significantly positively correlated with the SDI (Spearman's ρ=0.601, P<0.001).

Conclusion: The geographic and demographic disparities in neck pain burden across US states indicate a need for targeted interventions.

Keywords: Neck pain; Epidemiology; Global Burden of Disease; United States

Introduction

Neck pain is clinically defined as pain in the posterior cervical region, extending from the nuchal line superiorly to the first thoracic spinous process inferiorly, with or without radiation to the upper extremities [1]. It is widely associated with restricted cervical mobility and impaired daily functioning [2]. Neck pain is a major musculoskeletal condition worldwide, including in the United States [3], with recent estimates placing global age-standardized prevalence among adults at approximately 2.7% [4]. Its chronic, recurrent course imposes substantial personal, societal, and economic burdens. In the United States, low back and neck pain accounted for the highest spending among 154 health conditions studied, reaching an estimated $134.5 billion in 2016 [5]. Common musculoskeletal pain conditions have also been estimated to cost US employers approximately $61.2 billion annually in lost productive time [6]. Musculoskeletal conditions, including neck pain, are among the leading contributors to disability, accounting for a substantial burden measured in years lived with disability (YLD) [3,7].

The Global Burden of Disease (GBD) Study 2021, conducted by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, is among the most comprehensive efforts to quantify health loss systematically worldwide. It covers

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371 diseases and injuries across 204 countries and territories from 1990 to the present [8,9]. Neck pain burden varies considerably across US states, potentially reflecting differences in demographic composition, socioeconomic factors, healthcare access, and occupational exposure [9,10]. This variation is particularly relevant in the context of population aging and interstate disparities in healthcare access [8,11,12]. Although global and national studies have characterized neck pain trends [2,4,13], existing US-focused analyses remain limited: national survey data on general pain cover only 2002–2018 [12], and state-level neck pain assessments have used a single year of Google search-volume data as a behavioral proxy rather than direct epidemiological burden estimates [14]. Similarly, US-focused resources such as the Burden of Musculoskeletal Diseases in the US report rely primarily on healthcare utilization data—clinic visits and hospital discharges—reported as periodic, multiyear snapshots rather than continuously modeled, comparable state-level epidemiological estimates spanning 3 decades [3]. This study therefore aimed to evaluate neck pain burden systematically across all US states from 1990 to 2021 using validated metrics from the GBD Study 2021.

Methods

Data source and study population

Neck pain burden was analyzed using the GBD 2021 dataset in accordance with the Guidelines for Accurate and Transparent Health Estimates Reporting [15]. Because the GBD Study uses de-identified data, informed consent was not required. This study was approved by the Institutional Review Board (IRB) of Ewha Womans University Seoul Hospital (IRB no. SEUMC 2023-10-040).

Neck pain data were obtained from the GBD 2021 database, which contained epidemiological estimates for 371 diseases and injuries across 21 GBD regions and 204 countries and territories for 1990–2021. The data were accessed through the Global Health Data Exchange (https://ghdx.healthdata.org). Estimates for all 50 US states and the District of Columbia were included in the analysis.

Case definition

Neck pain was defined as cervical pain lasting at least 1 day, with or without radiation to the upper extremities [1]. The neck was defined as the posterior region extending from the nuchal line superiorly to the first thoracic spinous process inferiorly. Neck pain codes in the International Classification of Diseases, 10th Revision, covered cervicalgia (M54.2), cervical disc disorders (M50), and cervicocranial and cervicobrachial syndromes (M53.0–M53.1). Other disorders of the cervical region were coded as 723 in the International Classification of Diseases, Ninth Revision.

GBD estimates were generated from multiple population-based data sources using the standardized IHME modeling framework. Additional US data came from the Medical Expenditure Panel Survey (MEPS), Medicare administrative claims, and state health department records. Systematic bias in nonreference US data sources was adjusted using crosswalks estimated by meta-regression—Bayesian, regularized, trimmed [8].

Variables

Introduced by the IHME in 2015, the sociodemographic index (SDI) is a composite measure of developmental status across countries and regions. It is derived from average income, educational attainment, and fertility rates and incorporates the association between social progress and population health outcomes [16]. Although all US states were in the high-SDI quintile (>0.81), meaningful variation remained within this narrow range. The analysis therefore examined whether these within-band differences were associated with neck pain burden, without assuming that the findings would generalize to lower-SDI settings outside the United States [10].

Statistical analysis

GBD estimates were modeled using DisMod-MR ver. 2.1 (Institute for Health Metrics and Evaluation, University of Washington), a Bayesian meta-regression framework that uses a compartmental disease model based on differential equations to enforce internal consistency among prevalence, incidence, and remission. This ensures that estimates of each epidemiological parameter are mathematically coherent with the others [9,10]. All estimates are reported with 95% uncertainty intervals (UIs) derived from 500 data draws, with the 97.5th and 2.5th percentiles defining the upper and lower bounds, respectively [10]. Counts for the 4 US Census Bureau regions and 9 divisions were calculated by summing the counts of their constituent states, so that regional and divisional totals add up to the national total; because GBD does not publish region- or division-level estimates, the uncertainty bounds of these summed counts were obtained by summing state-level bounds and should be regarded as approximate.

Spearman's rank correlation was used to examine whether state-level variation in neck pain burden was associated with sociodemographic development, as measured by the SDI. Choropleth maps of burden were used to visualize spatial clustering and interstate disparities. Temporal trends in age-standardized rates over 1990–2021 were described by visually inspecting annual estimates. Given the descriptive, hypothesis-generating nature of

these state-level comparisons, uncorrected P-values are reported throughout, as discussed further in the limitations section.

Results

Neck pain burden trajectory across US states: 1990–2021

Neck pain ranked 16th among the leading causes of disability in the United States in 1990, 18th in 2010, and 14th in 2021. Its ranking thus rose overall during the study period, and it remained among the leading musculoskeletal contributors to disability [8].

In 2021, prevalent cases totaled 9.43 million (95% UI, 7.40–11.59 million), an increase of 41.17% (95% UI, 33.95%–48.92%) from 1990. In contrast, the age-standardized prevalence rate decreased marginally to 2,397.27 per 100,000 (95% UI, 1,850.62–3,002.28 per 100,000), a change of −0.20% (95% UI, −0.32% to −0.10%) (Supplement 1).

Incident cases likewise totaled 1.90 million (95% UI, 1.49–2.32 million) in 2021, an increase of 37.44% (95% UI, 30.12%–45.41%) from 1990. The age-standardized incidence rate, however, declined slightly to 506.12 per 100,000 (95% UI, 397.88–614.23 per 100,000), a change of −0.11% (95% UI, −0.18% to −0.06%) (Supplement 2).

Absolute YLD estimates increased from 0.66 million in 1990 to 0.92 million (95% UI, 0.62–1.30 million) in 2021, an increase of 38.72% (95% UI, 31.55%–46.36%). In contrast, the age-standardized YLD rate decreased by 1.12% (95% UI, −2.02% to −0.22%) to 236.52 per 100,000 (95% UI, 157.55–342.46 per 100,000) in 2021 (Supplements 3–5).

Regional and divisional patterns in neck pain burden, 1990–2021

Neck pain burden varied among the major US geographic regions over 1990–2021. The Northeast, Midwest, and South had small reductions in age-standardized prevalence and incidence rates, but no significant changes in YLD rates. In the West, none of the 3 rates changed significantly (Table 1, Supplement 6).

Among divisions, East South Central had the highest age-standardized prevalence rate in 2021, at 2,409.01 per 100,000 (95% UI, 1,862.14–3,014.77), whereas South Atlantic had the lowest, at 2,363.83 per 100,000 (95% UI, 1,815.53–2,970.66). The same divisions had the highest and lowest age-standardized incidence rates: 507.95 per 100,000 (95% UI, 399.26–615.80) in East South Central and 500.77 per 100,000 (95% UI, 392.13–610.55) in South Atlantic. The age-standardized YLD rate was highest in New England, at 238.03 per 100,000 (95% UI, 158.38–342.23), and lowest in South Atlantic, at 233.00 per 100,000 (95% UI, 153.18–337.40) (Table 1).

From 1990 to 2021, West South Central had the largest relative reductions in age-standardized prevalence (−0.28%; 95% UI, −0.40% to −0.15%) and incidence rates (−0.16%; 95% UI, −0.25% to −0.09%). Age-standardized YLD measures, however, showed no statistically significant changes (Table 1).

State-level variations in neck pain burden, 1990–2021

Neck pain burden varied considerably across US states in 2021. Age-standardized prevalence rates per 100,000 were highest in the District of Columbia (2,418.69; 95% UI, 1,872.06–3,028.00), Georgia (2,414.23; 95% UI, 1,866.65–3,022.25), and Delaware (2,411.57; 95% UI, 1,863.91–3,019.02). North Carolina had the lowest rate (2,117.28; 95% UI, 1,562.06–2,727.70) (Table 1, Fig. 1, Supplements 7, 8).

Age-standardized incidence rates followed a similar geographic pattern. Rates per 100,000 were highest in the District of Columbia (509.91; 95% UI, 400.68–618.27), Georgia (508.73; 95% UI, 399.78–616.77), and Delaware (508.22; 95% UI, 399.47–616.16), and lowest in North Carolina (462.03; 95% UI, 353.71–582.12) (Table 1, Fig. 1, Supplements 9, 10).

Age-standardized YLD rates per 100,000 indicated the highest disability burden in the District of Columbia (239.24; 95% UI, 158.86–344.07), Georgia (238.18; 95% UI, 157.67–341.69), and Delaware (237.28; 95% UI, 156.90–341.21). North Carolina had the lowest YLD rate (209.18; 95% UI, 135.10–316.54) (Table 1, Fig. 1, Supplements 10, 11).

State-level trends differed over 1990–2021. The largest significant reductions in age-standardized prevalence rates occurred in Wyoming (−0.49%; 95% UI, −0.68 to −0.31), West Virginia (−0.47%; 95% UI, −0.66 to −0.29), and Louisiana (−0.44%; 95% UI, −0.61 to −0.27). Age-standardized incidence rates also declined in these states, by −0.34%, −0.29%, and −0.28%, respectively. Conversely, Nevada had significant increases in both prevalence and incidence rates (+0.22%; 95% UI, 0.13–0.32) (Table 1, Fig. 1).

Visual inspection of the 1990–2021 trends showed a consistent U-shaped pattern in age-standardized prevalence, incidence, and YLD rates for neck pain across US divisions (Fig. 2).

Sex- and age-specific patterns in neck pain burden

In 2021, all neck pain metrics were higher in females than in males. Age-standardized prevalence was 2,700.48 per 100,000 (95% UI, 2,105.34–3,407.78) in females and 2,087.73 per 100,000 (95% UI, 1,578.93–2,621.24) in males. From 1990 to 2021, age-standardized prevalence rates declined slightly in both sexes despite increases in absolute case counts (Supplement 1).

Incidence rates showed a similar pattern by sex. In 2021,

Table 1. Counts, age-standardized rates, and percentage changes in neck pain prevalence, incidence, and years lived with disability in the United States

	Prevalence (95% UI)			Incidence (95% UI)			YLD (95% UI)		
	Absolute no., 2021	Age-standardized rate, per 100,000 people, 2021	Percentage change, 1990–2021	Absolute no., 2021	Age-standardized rate, per 100,000 people, 2021	Percentage change, 1990–2021	Absolute no., 2021	Age-standardized rate, per 100,000 people, 2021	Percentage change, 1990–2021
USA	9,430,459.08 (7,397,000.55–11,590,635.22)	2,397.27 (1,850.62–3,002.28)	−0.20% (−0.32 to −0.10)	1,904,357.69 (1,493,203.04–2,320,318.77)	506.12 (397.88–614.23)	−0.11% (−0.18 to −0.06)	919,636.54 (618,463.09–1,301,733.09)	236.52 (157.55–342.46)	−1.12% (−2.02 to −0.22)
Region									
Northeast	1,675,676.96 (1,316,537.01–2,061,505.89)	2,408.33 (1,861.49–3,014.08)	−0.18% (−0.30 to −0.07)	335,417.46 (263,128.49–409,032.00)	507.81 (399.14–615.64)	−0.12% (−0.21 to −0.04)	163,018.71 (109,213.79–229,215.27)	237.41 (157.42–342.62)	−1.06% (−3.83 to 1.80)
Midwest	1,956,325.46 (1,538,182.37–2,402,797.79)	2,405.47 (1,859.10–3,009.82)	−0.24% (−0.35 to −0.12)	394,564.61 (309,652.40–480,065.65)	507.47 (398.92–615.17)	−0.14% (−0.21 to −0.07)	190,554.02 (127,942.42–270,069.38)	237.27 (157.31–343.48)	−1.17% (−4.01 to 1.74)
South	3,561,588.44 (2,789,143.50–4,397,409.95)	2,384.03 (1,836.53–2,990.02)	−0.19% (−0.32 to −0.07)	721,483.72 (565,325.60–879,466.55)	504.01 (395.38–612.84)	−0.10% (−0.19 to −0.02)	347,089.90 (231,787.61–492,812.36)	234.97 (155.18–340.66)	−1.29% (−4.14 to 1.70)
West	2,236,868.21 (1,760,241.06–2,761,260.99)	2,403.17 (1,857.14–3,006.66)	−0.10% (−0.20 to 0.00)	452,891.89 (356,008.45–550,939.96)	507.09 (398.65–614.72)	−0.05% (−0.13 to 0.03)	218,973.92 (147,594.07–310,862.07)	237.65 (159.08–344.34)	−0.95% (−3.79 to 1.97)
Division									
New England	446,118.20 (349,872.16–548,393.47)	2,408.26 (1,861.34–3,014.12)	−0.16% (−0.27 to −0.04)	88,997.35 (69,904.71–108,752.82)	507.81 (399.15–615.63)	−0.11% (−0.20 to −0.03)	43,498.57 (29,183.10–61,117.65)	238.03 (158.38–342.23)	−0.98% (−3.77 to 1.96)
South Atlantic	1,880,004.62 (1,466,755.24–2,324,278.74)	2,363.83 (1,815.53–2,970.66)	−0.12% (−0.25 to −0.01)	379,830.73 (297,155.67–464,279.89)	500.77 (392.13–610.55)	−0.05% (−0.15 to 0.03)	182,934.78 (122,054.19–258,992.69)	233.00 (153.18–337.40)	−1.15% (−3.98 to 1.84)
East South Central	550,630.53 (433,315.46–676,597.74)	2,409.01 (1,862.14–3,014.77)	−0.25% (−0.37 to −0.13)	111,071.93 (87,024.04–135,385.45)	507.95 (399.26–615.80)	−0.14% (−0.22 to −0.07)	53,453.54 (35,784.91–75,340.44)	236.63 (157.15–343.20)	−1.53% (−4.55 to 1.52)
West South Central	1,130,953.32 (889,072.82–1,396,533.49)	2,406.06 (1,859.60–3,010.74)	−0.28% (−0.40 to −0.15)	230,581.07 (181,145.90–279,801.21)	507.51 (398.94–615.25)	−0.16% (−0.25 to −0.09)	110,701.58 (73,948.51–158,479.23)	237.48 (157.60–344.93)	−1.36% (−4.08 to 1.54)
State									
District of Columbia	20,434.58 (15,781.24–25,472.37)	2,418.69 (1,872.06–3,028.00)	−0.18% (−0.42 to 0.03)	4,104.72 (3,187.07–5,143.15)	509.91 (400.68–618.27)	0.01% (−0.16 to 0.17)	2,011.58 (1,333.48–2,887.79)	239.24 (158.86–344.07)	−0.76% (−3.61 to 2.09)
Georgia	304,380.90 (239,793.30–375,891.13)	2,414.23 (1,866.65–3,022.25)	0.04% (−0.09 to 0.15)	61,579.98 (48,296.90–75,022.28)	508.73 (399.78–616.77)	0.06% (−0.06 to 0.16)	29,756.29 (19,990.54–42,326.97)	238.18 (157.67–341.69)	−0.82% (−3.66 to 2.11)

(Continued to the next page)

Table 1. Continued

	Prevalence (95% UI)			Incidence (95% UI)			YLD (95% UI)		
	Absolute no., 2021	Age-standardized rate, per 100,000 people, 2021	Percentage change, 1990–2021	Absolute no., 2021	Age-standardized rate, per 100,000 people, 2021	Percentage change, 1990–2021	Absolute no., 2021	Age-standardized rate, per 100,000 people, 2021	Percentage change, 1990–2021
Delaware	28,839.58 (22,731.33–35,324.88)	2,411.57 (1,863.91–3,019.02)	−0.05% (−0.13 to 0.03)	5,786.30 (4,541.04–7,051.12)	508.22 (399.47–616.16)	−0.06% (−0.13 to 0.01)	2,796.42 (1,876.34–3,947.11)	237.28 (156.90–341.21)	−1.06% (−4.02 to 1.87)
North Carolina	262,446.99 (194,268.32–336,478.96)	2,117.28 (1,562.06–2,727.70)	0.02% (−0.10 to 0.11)	54,918.22 (41,729.13–68,088.33)	462.03 (353.71–582.12)	0.06% (−0.01 to 0.12)	25,618.37 (16,589.14–37,278.85)	209.18 (135.10–316.54)	−1.04% (−3.86 to 2.13)
Wyoming	16,019.06 (12,584.79–19,607.87)	2,389.95 (1,845.52–2,987.94)	−0.49% (−0.68 to −0.31)	3,255.85 (2,566.95–3,967.72)	505.16 (397.29–612.28)	−0.34% (−0.49 to −0.21)	1,560.11 (1,056.88–2,182.99)	235.46 (157.69–337.86)	−1.53% (−4.20 to 1.28)
West Virginia	51,882.55 (40,813.57–63,557.33)	2,401.68 (1,855.75–3,004.27)	−0.47% (−0.66 to −0.29)	10,388.75 (8,197.09–12,701.63)	506.90 (398.53–614.46)	−0.29% (−0.42 to −0.17)	4,988.65 (3,378.14–6,976.26)	234.68 (156.67–338.49)	−2.18% (−5.05 to 0.85)
Louisiana	129,281.67 (101,436.09–158,870.70)	2,405.46 (1,859.22–3,009.90)	−0.44% (−0.61 to −0.27)	26,195.50 (20,573.18–31,915.60)	507.41 (398.88–615.12)	−0.28% (−0.39 to −0.18)	12,574.41 (8,444.69–17,733.97)	236.49 (157.65–342.28)	−1.52% (−4.29 to 1.25)
Nevada	89,378.85 (70,428.82–110,592.38)	2,402.00 (1,856.35–3,004.92)	0.22% (0.13 to 0.32)	18,068.06 (14,201.51–21,991.34)	507.07 (398.65–614.61)	0.15% (0.06 to 0.23)	8,721.49 (5,886.57–12,374.48)	236.61 (159.03–341.18)	−0.75% (−3.68 to 2.38)

Selected US Census Bureau divisions are shown; data for all 9 divisions are provided in Supplement 6. Region and division counts and their uncertainty bounds are the sums of the corresponding values of their constituent states (state values in Supplement 6); because GBD does not publish region- or division-level estimates, the summed bounds are approximate. The 9 division totals add up to the US total.
UI, uncertainty interval; YLD, years lived with disability.

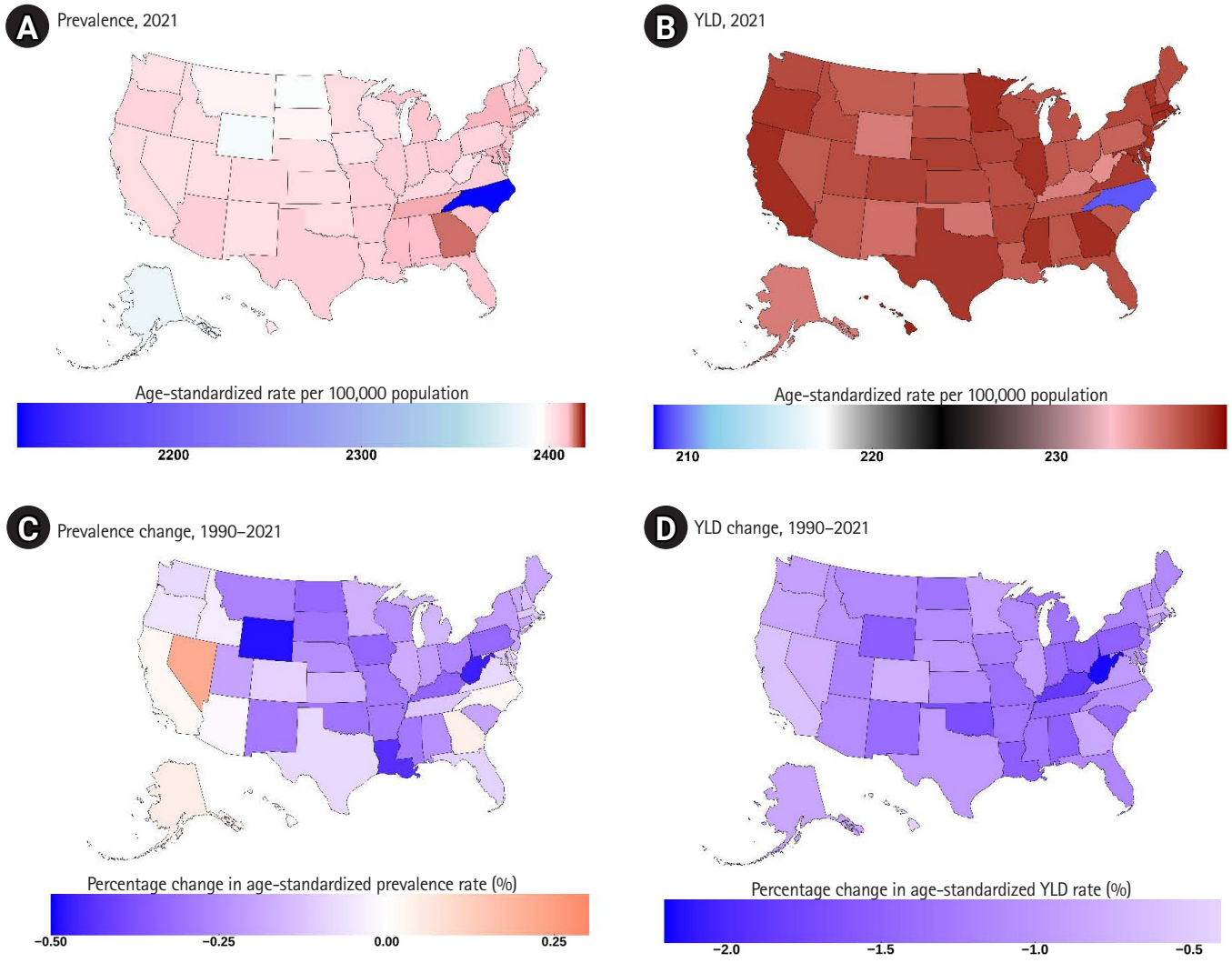


Fig. 1. State-level distribution and temporal changes in age-standardized prevalence and years lived with disability (YLD) rates for neck pain in the United States, 1990–2021. (A) Age-standardized prevalence rate per 100,000 in 2021; (B) age-standardized YLD rate per 100,000 in 2021; (C) percentage change in age-standardized prevalence rate, 1990–2021; and (D) percentage change in age-standardized YLD rate, 1990–2021. Panels (A) and (B) show the highest rates in the District of Columbia, Georgia, and Delaware and the lowest in North Carolina, Alaska, and Wyoming. Panel (C) shows the largest decreases in age-standardized prevalence in Wyoming, West Virginia, and Louisiana, whereas Nevada shows an increase. Panel (D) shows declines in age-standardized YLD rates across most states.

age-standardized incidence was 555.04 per 100,000 (95% UI, 428.13–679.07) in females and 456.92 per 100,000 (95% UI, 360.91–553.57) in males. Both sexes had equivalent small declines in incidence rates over 1990–2021, despite increases in the absolute numbers of incident cases (Supplement 2).

Disability burden was also higher in females: the age-standardized YLD rate in 2021 was 265.07 per 100,000 (95% UI, 175.19–386.22), compared with 207.41 per 100,000 (95% UI, 136.37–303.02) in males. Neither sex had a statistically significant change in age-standardized YLD rates from 1990 to 2021, although absolute YLD increased (Supplements 3, 12). Fig. 3 illustrates these trends.

Peak ages differed by burden metric (Supplement 13). In both sexes, prevalence and YLD rates were highest at ages 45–49 years, whereas incidence peaked at ages 40–44 years (Fig. 4, Supplement 14).

Association with sociodemographic development

Supplement 15 presents the associations between SDI and neck pain burden across US states in 2021. SDI was significantly positively associated with age-standardized YLD rates (Spearman's $\rho = 0.60$, $P < 0.001$). In contrast, its correlations with

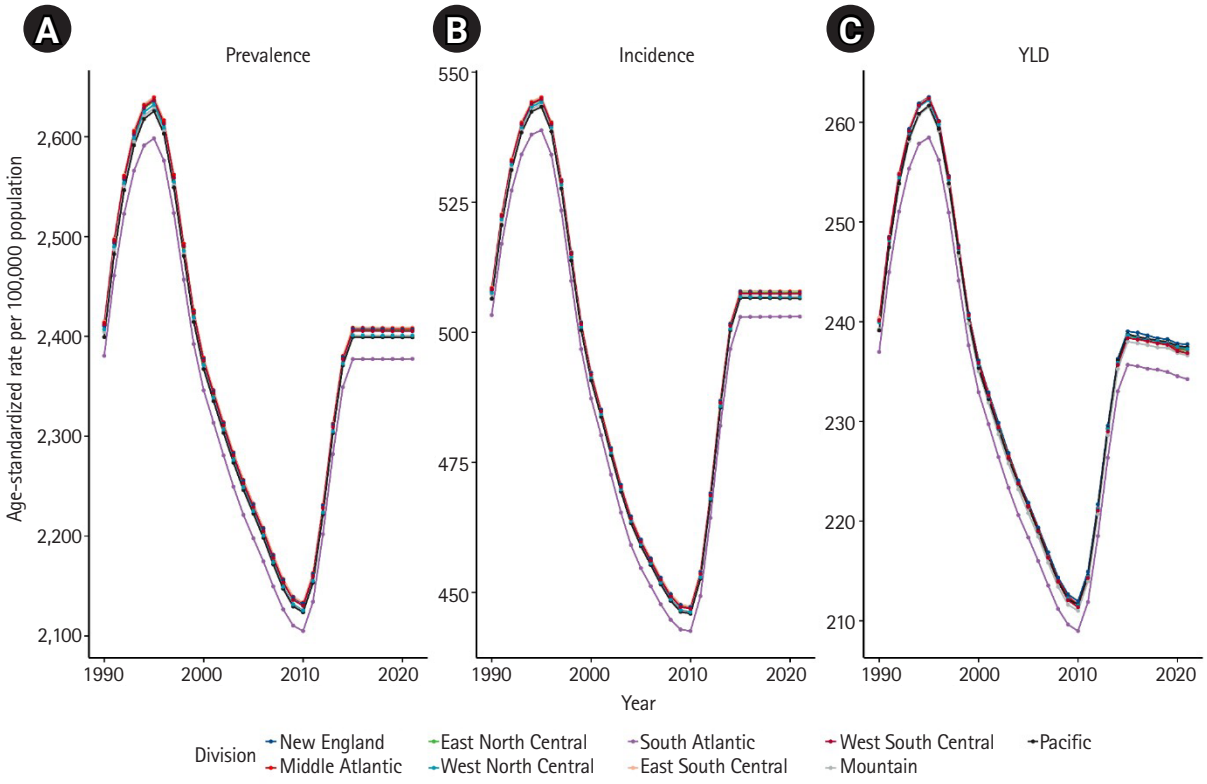


Fig. 2. (A–C) Temporal trends in age-standardized prevalence, incidence, and years lived with disability (YLD) rates for neck pain across United States divisions, 1990–2021. In all divisions, the 3 rates initially increased from 1990 to the early 2000s, then declined to their lowest levels around 2010 before increasing slightly or stabilizing. South Atlantic consistently had the lowest rates for all 3 metrics throughout the study period.

age-standardized prevalence ($\rho = 0.15$, $P = 0.29$) and incidence rates ($\rho = 0.15$, $P = 0.30$) were weak and not statistically significant. Nevertheless, the 4 East South Central states (Alabama, Kentucky, Mississippi, and Tennessee) and Georgia had a higher neck pain burden despite relatively lower SDI scores than other regions.

Discussion

Age-standardized prevalence and incidence rates for neck pain remained relatively stable over the 3-decade study period, whereas absolute case counts increased substantially, reflecting demographic shifts in the US population. The Midwest had the greatest reductions in both rates. Sex disparities persisted throughout the study period, with females consistently having higher rates than males across all metrics. Burden was highest in middle-aged individuals. Sociodemographic development was positively associated with neck pain burden, although regional differences were also evident.

The slight decline in age-standardized neck pain prevalence in the United States, alongside the substantial increase in absolute cases over 1990–2021, could reflect the combined effects of demographic shifts [17,18], healthcare access patterns [19,20], and changing risk factor profiles [4,21] in the United States. These trends contrast with global patterns over the same period [2,13,22], suggesting distinct epidemiological dynamics in the United States.

The U-shaped temporal pattern, with rates falling to a nadir around 2010 before rising again (Supplement 16), coincided with major changes in device use and work patterns. Smartphone ownership among US adults rose rapidly during this period, alongside increases in prolonged computer use and sedentary desk work. Given their known associations with neck pain risk, these are plausible contributors, although they were not directly tested [23].

Geographic variation in neck pain burden across US states likely reflects multiple factors operating at different scales. Burden was higher in the East South Central states (Alabama, Kentucky, Mississippi, and Tennessee) and Georgia. These areas overlap substantially with Appalachia and the southeastern United States, where disproportionately high prevalence of musculoskeletal disorders and chronic pain has been documented. These regions

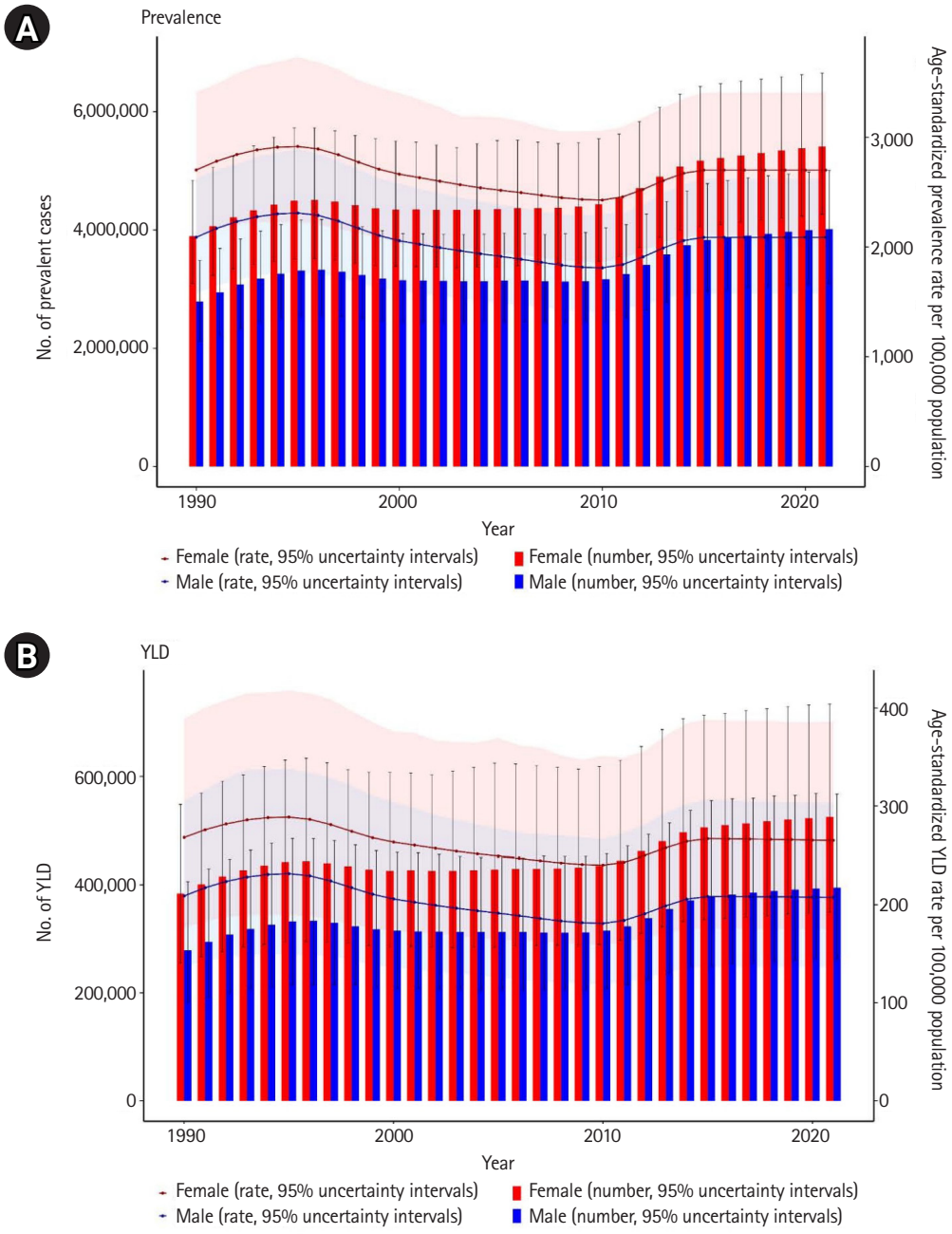


Fig. 3. (A, B) Counts and age-standardized prevalence and years lived with disability (YLD) rates for neck pain by sex in the United States, 1990–2021. Age-standardized prevalence and YLD rates declined slightly over the study period despite overall increases in absolute counts. Females had higher prevalence and YLD rates and absolute counts than males throughout the study period.

have lower socioeconomic status, more physically demanding occupations, and relatively limited healthcare access [12,14,19,24]. Historically, employment has been more concentrated in mining, manufacturing, and agriculture, which involve repetitive motion, heavy lifting, and prolonged awkward postures. Previous occupational health research has associated these exposures with musculoskeletal pain, including neck pain. Although this occupational profile offers a plausible context for the elevated burden in these states, the ecological, state-level design cannot establish a direct causal relationship between specific industries and individual neck pain risk [4,23].

Socioeconomic disparities may further exacerbate neck pain burden. Alabama, Kentucky, Mississippi, Tennessee, and Georgia had relatively low SDI scores compared with other US regions (Supplement 15). The lower educational attainment [25] and economic disadvantages [23,26] in these regions have been re-

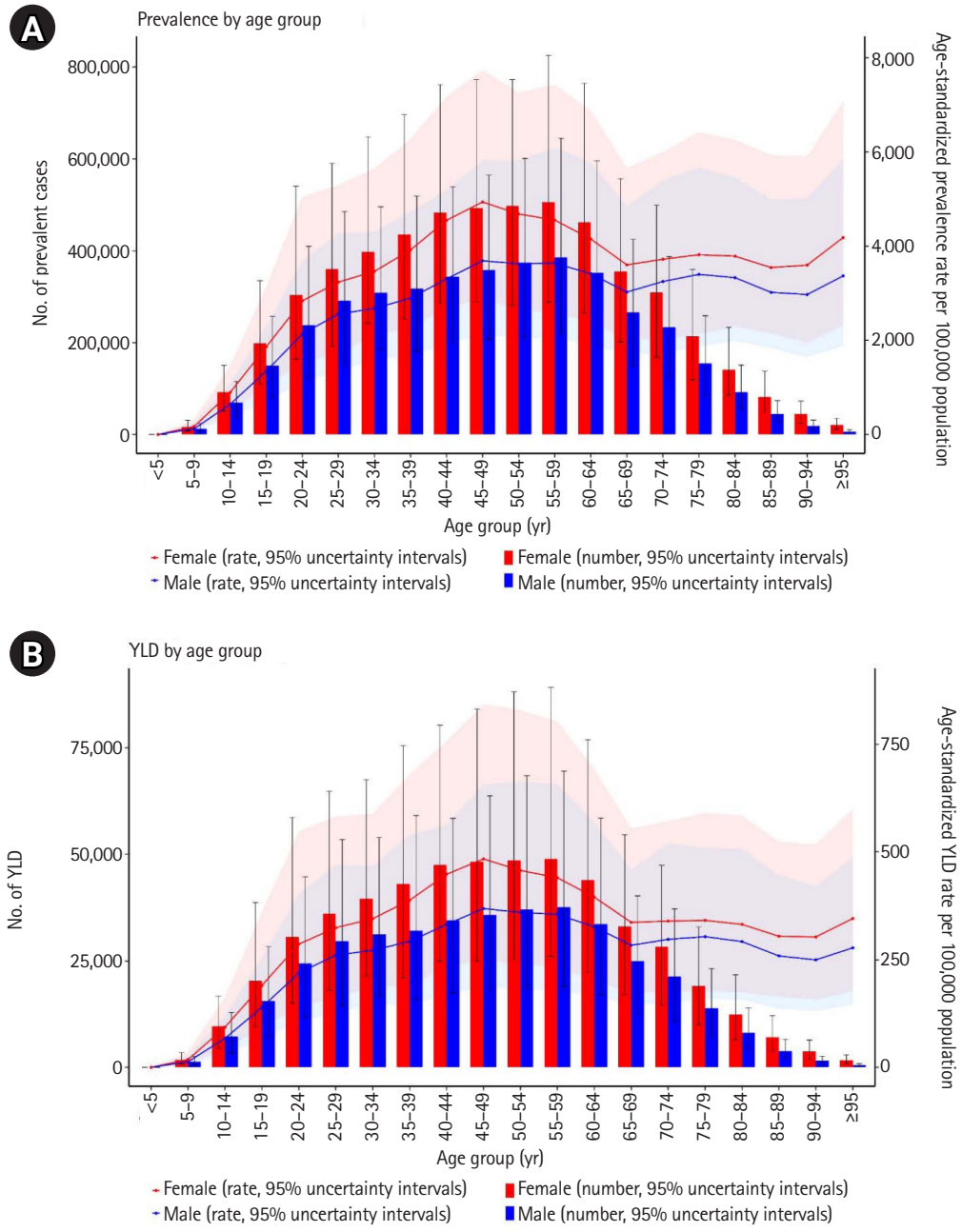


Fig. 4. (A, B) Counts and age-standardized prevalence and years lived with disability (YLD) rates for neck pain by age group and sex in the United States, 2021. Prevalence and YLD rates peaked in middle age in both sexes. Females had notably higher prevalence and YLD rates than males in most age groups.

ported to correlate with adverse health outcomes and a higher prevalence of chronic pain [12]. Obesity, smoking, and sedentary behaviors are also more common in these regions and have been associated with a higher prevalence of musculoskeletal pain [8]. Previous studies have likewise documented geographic clustering of pain conditions in the southern and Appalachian United States [11].

Previous studies have reported higher neck pain prevalence in females, with female-to-male ratios of 1.3–1.5 [2,22,27]. Biological and psychosocial factors may together explain this consistently higher burden. Smaller cervical vertebrae and distinct muscle mass distributions are anatomical differences that have been suggested to increase susceptibility to neck pain in females [28]. Pain sensitivity and inflammatory responses have been associated with hormonal influences, particularly estrogen fluctuations [29]. Higher rates of stress, depression, and anxiety among females may

also contribute to greater pain perception and disability [30]. The disparity may also partly reflect occupational exposure to prolonged computer use and repetitive tasks in service or healthcare work [23].

Population aging likely contributed to the rise in absolute case counts during the study period because neck pain burden peaks in middle age. As large birth cohorts entered the 45–64-year age range associated with the highest reported burden, this demographic shift would increase absolute case counts even if age-standardized rates remained stable or declined. This pattern is consistent with our finding of rising absolute burden alongside modestly declining age-standardized rates. Previous US survey analyses found the highest neck pain prevalence at ages 45–64 years, consistent with our results [31]. These findings indicate a need for age-specific prevention strategies and future healthcare planning.

SDI was significantly positively correlated with age-standardized YLD in this study. There are 2 possible explanations. YLD estimates use severity weights derived from MEPS [9], which may capture disability more effectively among populations seeking healthcare in more developed states. Alternatively, greater healthcare access in higher-SDI states may lead residents to report chronic pain and disability more often, without a true difference in case counts. These ecological data cannot distinguish between the 2 explanations. The finding agrees with previous GBD-based studies and research on other musculoskeletal disorders, such as back pain [7,22]. The higher prevalence and YLD associated with musculoskeletal pain in high-SDI countries, including the United States, also support this pattern [22]. Despite the overall positive global correlation, some studies have reported contrasting patterns in specific populations and regions. A global study, for example, found a negative correlation between SDI and neck pain burden in young and middle-aged adults [32]. A study of the Middle East and North Africa reported weak negative correlations in regions with intermediate SDI levels (approximately 0.62–0.82) [33]. In our study, the East South Central states and Georgia had a higher burden despite lower SDI scores. This agrees with US national data showing a higher burden of musculoskeletal disorders in socioeconomically disadvantaged populations [34,35]. Higher chronic pain prevalence in low-income southern regions, including Appalachia, suggests that the relationship between SDI and neck pain burden is not purely linear. Differences in population aging, occupational exposure, education, healthcare access, and cultural factors across US regions may explain this variability [1,6,13,22,24,34-38]. Together, these findings show the complex distribution of neck pain burden across US states and support multifaceted prevention and management strategies.

Study limitations

Several limitations should be considered when interpreting these findings. First, the analysis used modeled GBD estimates rather than direct population measurements, introducing uncertainty into burden estimates. DisMod-MR ver. 2.1 may not fully capture local differences in disease patterns or healthcare reporting, and state-level estimates may be uncertain where primary data are limited. Second, neck pain definitions and measurements varied among the studies used in GBD modeling. Self-reported pain is subject to recall bias and differences in healthcare-seeking behavior; variation in case definitions and assessment methods may also have introduced measurement error. Third, multiple statistical comparisons across 51 jurisdictions were conducted without formal adjustment for multiple testing, potentially increasing type I error, and spatial autocorrelation was not formally assessed. Fourth, the GBD framework may omit state-specific determinants, including occupational regulations, healthcare system characteristics, and environmental factors. Finally, state-level analysis may obscure within-state variation in urban–rural or local socioeconomic conditions, while the absence of individual-level data limits clinical interpretation. State-level policy differences (e.g., insurance coverage and workers' compensation) and the pandemic-related shift to remote work were not examined and may also have influenced the estimates.

Conclusion

Age-standardized neck pain rates in the United States declined modestly from 1990 to 2021, but absolute case counts rose substantially, largely driven by population aging into the 45–64-year age range of peak burden. Geographic disparities remained substantial: burden was highest in the District of Columbia, Georgia, and Delaware and lowest in North Carolina. These findings suggest that prioritizing middle-aged adults and the states with the highest burden may benefit prevention efforts and healthcare resource allocation.

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Authors' contribution

Conceptualization: YC, MSP, HKK, TJS. Data curation: YC,

MSP, HKK, TJS. Formal analysis: SP, DWS, JHP, TJS. Methodology: SP, DWS, JHP, TJS. Validation: SP, DWS, JHP, TJS. Project administration: YC, MSP, HKK, TJS. Funding acquisition: TJS. Writing–original draft: SP, DWS, JHP, TJS. Writing–review & editing: SP, DWS, JHP, TJS. Final approval of the manuscript: all authors.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

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None.

Data availability

The data supporting this study are publicly available through the Global Health Data Exchange, the IHME data catalog, at https://ghdx.healthdata.org. Estimates of neck pain prevalence, incidence, and YLD across US states for 1990–2021 can be queried and downloaded using the GBD Results Tool at https://vizhub.healthdata.org/gbd-results/

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None.

Supplementary materials

Supplementary files are available from https://doi.org/10.7910/DVN/4X4EHP

Supplement 1. Annual number of prevalent cases, age-standardized prevalence rates, and percentage change from 1990 to 2021, by sex.

Supplement 2. Annual number of incident cases, age-standardized incidence rates, and percentage change from 1990 to 2021, by sex.

Supplement 3. Annual number of YLD, age-standardized YLD rates, and percentage change from 1990 to 2021, by sex.

Supplement 4. Numbers, age-standardized rates, and percentage change of incidence, prevalence, and YLD from 1990 to 2021, in global and the United States.

Supplement 5. Annual trends of age-standardized rates and numbers for (A) prevalence, (B) incidence, (C) YLD from 1990 to 2021 (shaded areas represent 95% uncertainty intervals).

Supplement 6. Numbers, age-standardized rates, and percentage changes of prevalence, incidence, and YLD in the United States.

Supplement 7. Age-standardized prevalence rates in 1990, 2019, 2020, and 2021 and percentage change from 1990 to 2021.

Supplement 8. National age-standardized rates of prevalence in 2021, with percentage change from 1990 to 2021.

Supplement 9. Age-standardized incidence rates in 1990, 2019, 2020, and 2021 and percentage change from 1990 to 2021.

Supplement 10. National age-standardized rates of incidence and YLD in 2021, with percentage change from 1990 to 2021.

Supplement 11. Age-standardized YLD rates in 1990, 2019, 2020, and 2021 and percentage change from 1990 to 2021.

Supplement 12. Annual trends of age-standardized rates and numbers for (A) prevalence (B) incidence (C) YLD from 1990 to 2021, by sex (shaded areas represent 95% uncertainty intervals).

Supplement 13. Age-standardized prevalence, incidence, YLD rates in 2021, by age groups and sex.

Supplement 14. Total rates of (A) prevalence, (B) incidence, (C) YLD, by age groups and divisions.

Supplement 15. Age-standardized rates of (A) prevalence, (B) incidence, (C) YLD according to the sociodemographic index (SDI) in 2021, with linear regression (shaded areas represent 95% uncertainty intervals).

Supplement 16. Percentage change in age-standardized rates of (A) prevalence, (B) incidence, (C) YLD, from 2000 to 2010, and from 2010 to 2021.

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Global, regional, and national burden of motor neuron diseases, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021

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Purpose: Healthcare planning and resource allocation require accurate estimates of the burden of motor neuron diseases (MNDs). This study evaluated the global impact of MNDs from 1990 to 2021 as part of the Global Burden of Disease (GBD) Study 2021.
Methods: GBD 2021 data were used to assess the global burden of MNDs from 1990 to 2021 in terms of prevalence, incidence, disability-adjusted life years (DALYs), and deaths. The relationship between MND burden and the Socio-demographic Index (SDI) was also examined.
Results: Globally, MNDs accounted for 272,732 prevalent cases (95% uncertainty interval [UI], 236,195–313,676), 64,178 incident cases (95% UI, 58,506–70,270), 1,040,566 DALYs (95% UI, 963,064–1,123,956), and 39,082 deaths (95% UI, 35,757–42,433) in 2021. The corresponding age-standardized rates per 100,000 people were 3.31 (95% UI, 2.86–3.80) for prevalence, 0.46 (95% UI, 0.42–0.49) for mortality, and 12.17 (95% UI, 11.24–13.15) for DALYs. From 1990 to 2021, the numbers of prevalent and incident cases increased, but their age-standardized rates decreased by 1.36% and 4.69%, respectively. By contrast, the age-standardized mortality rate increased by 19.84%. MND burden was generally higher in regions with a high SDI, although rates in high-income Asia Pacific were relatively low compared with those in regions with similar SDI values.
Conclusion: From 1990 to 2021, the absolute burden of MNDs increased, age-standardized prevalence and incidence rates declined slightly, and mortality-related burden increased. These trends underscore the need for evidence-based national and global healthcare planning. Geographic variation in MND burden may reflect regional differences in the roles of sociodemographic and genetic factors.

Keywords: Disability-adjusted life years; Global Burden of Disease; Global; Incidence; Motor neuron diseases; Prevalence

Introduction

Background/rationale

Motor neuron diseases (MNDs) are rare neurological conditions characterized by progressive motor neuron degeneration that affects the upper and lower extremities [1]. They include hereditary spastic paraplegia, spinal muscular atrophy, amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, progressive pseudobulbar palsy, and muscular atrophy. ALS is the most common; within 2 years of diagnosis, 50% of people with ALS develop respiratory failure [1,2].

Despite numerous epidemiological studies in Europe and the

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United States, the rarity of MNDs has limited understanding of their prevalence, incidence, and overall impact [3-6]. ALS incidence peaks around age 70; its prevalence is 4.5 per 100,000 individuals and its incidence rate is 1.7 per 100,000 person-years [7,8]. The Global Burden of Disease (GBD) Study 2016 reported an all-age incidence rate of 0.78 per 100,000 person-years and high age-standardized prevalence in economically advanced regions, including Australasia, North America, and Europe, but not Asia Pacific [9]. Previous prediction models suggested that global MND prevalence would decline modestly by 2040, whereas population aging would continue to increase incidence, deaths, and disability-adjusted life years (DALYs) [10]. Nevertheless, recent, detailed epidemiological data at global, regional, and national levels remain limited.

Objectives

This study assessed the global burden of MNDs from 1990 to 2021 using GBD estimates of prevalence, incidence, DALYs, years lived with disability (YLDs), years of life lost (YLLs), and deaths, stratified by sex, age, region, and country. It also examined MND burden in relation to the Socio-demographic Index (SDI), a measure of national development. The manuscript was prepared as part of the GBD Collaborator Network in accordance with the GBD Protocol.

Methods

Ethics statement

The study followed the Declaration of Helsinki and received approval from the Institutional Review Board of Ewha Womans University Seoul Hospital (EUMC 2023-10-040; approved November 3, 2023). Patient consent was waived because the study used secondary, de-identified data.

Study design

MND data were obtained from GBD 2021, which provides epidemiological estimates for 371 diseases and injuries across 21 GBD regions and 204 countries and territories from 1990 to 2021. These data are freely available through the Global Health Data Exchange (GHDx) [11]; previous reports provide detailed descriptions of the data, methods, and statistical modeling [11,12]. The data used in this study were anonymous and publicly accessible.

Setting

MNDs comprise chronic, degenerative, and relentlessly progressive motor-system disorders characterized by selective loss of upper and lower motor neurons and consequent failure of voluntary musculature. To quantify their population burden, the Institute for Health Metrics and Evaluation (IHME) systematically synthesized the evidence and analyzed administrative claims coded using the International Classification of Diseases (ICD), specifically ICD-9 codes 335–335.9 and ICD-10 codes G12–G12.9. GBD reports these data as a single composite MND category [9,13,14].

Variables

Mortality

MND mortality was analyzed with the Cause of Death Ensemble Model (CODEm), which is used across GBD studies. The model incorporated 14,165 site-years, representing specific combinations of locations and years, and several predictive covariates. The covariates used to model MND mortality are available through GHDx (https://www.healthdata.org/gbd/methods-appendices-2021/motor-neuron-disease). They included cholesterol concentrations, fruit consumption, asbestos manufacturing, latitude, the proportion of people with access to sanitation and safe drinking water, healthcare availability and efficiency, educational attainment, disparity-adjusted and log-transformed income, and the SDI [15,16]. CODEm identifies predictive covariates through a comprehensive literature review of disease associations, whether or not those associations are causal. It determines the optimal combination of covariates for predicting mortality rates using sources such as verbal autopsy reports and vital statistics records [15,16]. Supplement 1 also describe MND severity and YLDs in detail.

Disability-adjusted life years

GBD 2021 estimated MND burden primarily with DisMod-MR ver. 2.1 (Institute for Health Metrics and Evaluation), a Bayesian meta-regression platform for disease modeling. The model integrated prevalence, incidence, cause-specific mortality from the GBD cause-of-death ensemble, and excess mortality estimated as cause-specific mortality divided by prevalence. Prespecified structural constraints included no remission at any age and an incidence upper bound of 0.0004. To avoid artificially exaggerating regional heterogeneity, bounds were imposed on the super-region random effects, restricting prevalence to −0.5 and incidence to 0.5 [17]. Preliminary YLDs were calculated by multiplying the prevalence of each long-term outcome by its corresponding composite disability weights. These estimates were then adjusted for comorbidities through a simulation covering all causes in GBD 2021. YLLs were calculated by multiplying deaths in

each age group by the corresponding remaining life expectancy from the standard life table used in previous GBD 2021 studies [11,12]. DALYs were calculated as the sum of YLLs and YLDs.

Socio-demographic index

Introduced by IHME in 2015, the SDI is a composite measure of national or regional development that emphasizes the relationship between social progress and population health. It is calculated as the geometric mean of 3 indicators, each standardized to a scale of 0 to 1: the total fertility rate among people younger than 25 years, mean educational attainment among people aged 15 years or older, and lag-distributed income per capita. In GBD 2021, SDI values ranged from 0 to 1: 0 represented the lowest education and income levels and highest fertility rate, whereas 1 represented the highest education and income levels and lowest fertility rate. The 204 countries and territories were classified into 5 SDI quintiles: low (< 0.46), low-middle (0.46–0.60), middle (0.61–0.69), high-middle (0.70–0.81), and high (> 0.81). Lower SDI values indicate a lower level of social development [11,12].

Data sources and measurement

GBD 2021 analyzed systematic reviews of multiple data sources alongside the US National Health and Nutrition Examination Survey, National Health Interview Survey, and additional national claims database data [18,19]. IHME at the University of Washington excluded studies or datasets with small samples (< 150), non-population samples, review articles, or unclear subpopulation definitions [18,19]. Earlier research describes the procedures for collecting nonfatal-outcome and mortality data in detail. MND-related DALYs, YLDs, YLLs, and deaths were estimated using health claims data, survey microdata, registries, surveillance systems, and systematic evaluations of reports, regardless of publication status [18]. Supplement 1 provides an overview of MNDs in GBD and the detailed search terms.

Bias

Interpretation of these findings requires consideration of several potential biases, particularly those inherent in GBD. MND case ascertainment is difficult, and under-recognition may have occurred, especially among older adults and ethnic minority populations. Because IHME provides pooled estimates for all MND phenotypes, differences between subtypes could not be assessed. Inputs came primarily from ICD-coded administrative data and systematic reviews rather than cluster-random samples, limiting the robustness of state-level comparisons and potentially introducing selection and information bias.

Statistical methods

Estimates were presented with 95% uncertainty intervals (UIs), obtained by resampling the data 500 times. The lower and upper limits corresponded to the 2.5th and 97.5th percentiles of the resulting uncertainty distribution, respectively [11,12]. The health impact of MNDs was assessed using prevalence, incidence, DALYs, YLDs, YLLs, deaths, and their corresponding rates. Burden estimates were accompanied by 95% UIs to ensure accuracy and reliability [11,12]. The GBD dataset contains populations with diverse age distributions, making adjustment for age structure essential. GBD 2021 therefore calculated age-standardized rates per 100,000 people to allow comparisons between populations with different age structures. Analyses were performed using R ver. 4.4.2 (The R Foundation for Statistical Computing).

Results

Main results

Global burden of motor neuron diseases in 2021 by region

Table 1 and Supplement 2 (Table S1) present MND burden counts and percentage changes in age-standardized rates for both sexes by region from 1990 to 2021. Fig. 1 shows age-standardized DALY rates in the 21 GBD regions, while Supplement 3 (Figs. S1–S5) present age-standardized prevalence, incidence, DALYs, YLDs, YLLs, and deaths by year, sex, and age group. Over time, incidence rates decreased in females but remained stable in males, whereas YLL rates increased in males but remained stable in females. High-income Commonwealth regions and Australasia had the largest sex differences across all measures (Fig. S6 of Supplement 3).

Table 2 and Supplement 3 (Figs. S7–S11) present counts and age-standardized rates for MND prevalence, incidence, DALYs, YLDs, YLLs, and mortality by GBD region in 1990 and 2021, together with percentage changes in age-standardized rates over this period. In 2021, an estimated 272,732 people (95% UI, 236,195–313,676) were living with MNDs worldwide, a 68.4% increase from 161,926 (95% UI, 137,006–189,263) in 1990. Incident cases increased to 64,178 (95% UI, 58,506–70,270) in 2021, although the age-standardized incidence rate decreased by 4.69% to 0.77 per 100,000 people (95% UI, 0.70–0.84). The global burden was 1,040,566 DALYs (95% UI, 963,064–1,123,956), with an age-standardized rate of 12.17 per 100,000 people (95% UI, 11.24–13.15). YLDs totaled 57,889 (95% UI, 40,687–78,031), and YLLs totaled 982,677 (95% UI, 904,588–1,064,644). MNDs accounted for 39,082 deaths worldwide in 2021 (95% UI, 35,757–42,433), corresponding to an age-standardized mortality

Table 1. Global counts, age-standardized rates, and percentage changes in prevalence, incidence, DALYs, YLDs, YLLs, and mortality for motor neuron diseases in both sexes, 1990–2021

Motor neuron disease	Age-standardized rate 1990	Age-standardized rate 2019	Age-standardized rate 2020	Age-standardized rate 2021	Change from 1990 to 2021 (%)	Total, 1990	Total, 2019	Total, 2020	Total, 2021	Change from 1990 to 2021 (%)
Incidence	0.81 (0.72 to 0.9)	0.78 (0.71 to 0.85)	0.77 (0.70 to 0.84)	0.77 (0.7 to 0.84)	−4.69 (−6.53 to −2.86)	36,769.25 (33,067.78 to 41,299.83)	62,369.32 (56,986.93 to 68,228.92)	63,305.35 (57,741.11 to 69,237.58)	64,177.73 (58,506.16 to 70,270.30)	74.54 (69.32 to 79.22)
Prevalence	3.36 (2.87 to 3.92)	3.34 (2.89 to 3.83)	3.32 (2.88 to 3.82)	3.31 (2.86 to 3.80)	−1.36 (−3.28 to 0.87)	161,926.07 (137,005.78 to 189,262.55)	266,423.27 (230,321.68 to 306,134.58)	269,745.40 (233,062.22 to 310,601.97)	272,732.25 (236,194.50 to 313,676.27)	68.43 (61.82 to 76.16)
Deaths	0.38 (0.36 to 0.4)	0.46 (0.43 to 0.49)	0.45 (0.41 to 0.48)	0.46 (0.42 to 0.49)	19.84 (10.79 to 30.39)	15,260.07 (14,366.61 to 16,042.60)	37,597.36 (34,931.4 to 39,641.17)	37,970.60 (34,766.10 to 40,469.18)	39,081.64 (35,756.51 to 42,432.82)	156.10 (135.92 to 179.39)
DALYs	11.22 (10.39 to 11.98)	12.37 (11.55 to 13.14)	12.14 (11.25 to 13.05)	12.17 (11.24 to 13.15)	8.42 (−0.78 to 18.64)	506,146.42 (462,034.99 to 545,049.77)	1,013,712.88 (948,249.20 to 1,075,784.85)	1,017,006.24 (943,075.42 to 1,092,175.94)	1,040,565.98 (963,064.26 to 1,123,956.29)	105.59 (86.69 to 126.09)
YLDs	0.71 (0.5 to 0.97)	0.71 (0.5 to 0.96)	0.71 (0.50 to 0.96)	0.70 (0.49 to 0.96)	−1.49 (−3.45 to 0.70)	34,425.85 (23,884.86 to 47,211.93)	56,556.62 (39,699.29 to 76,267.04)	57,254.43 (40,229.05 to 77,249.01)	57,889.10 (40,686.61 to 78,030.59)	68.16 (61.65 to 75.90)
YLLs	10.51 (9.70 to 11.2)	11.66 (10.84 to 12.36)	11.43 (10.57 to 12.26)	11.46 (10.52 to 12.43)	9.10 (−0.70 to 19.99)	471,720.57 (427,708.75 to 507,715.98)	957,156.26 (890,565.78 to 1,015,265.18)	959,751.80 (887,828.67 to 1,028,242.44)	982,676.88 (904,588.13 to 1,064,643.84)	108.32 (88.16 to 129.79)

All age-standardized rates are reported per 100,000 people.
DALYs, disability-adjusted life years; YLDs, years lived with disability; YLLs, years of life lost.

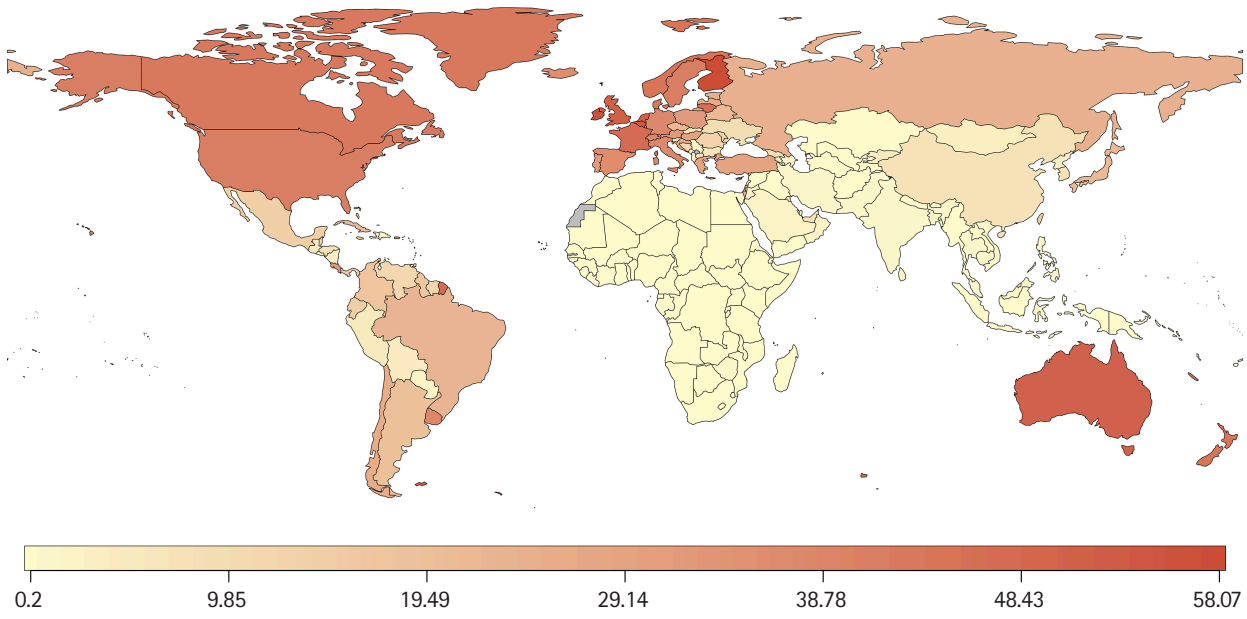


Fig. 1. Global age-standardized disability-adjusted life year (DALY) rates per 100,000 people.

rate of 0.46 per 100,000 people (95% UI, 0.42–0.49). Overall, age-standardized prevalence and incidence rates declined slightly, whereas mortality, YLL, and DALY rates increased.

Age-standardized prevalence rates were numerically high in regions such as Western Europe and high-income North America, but low in Central, Eastern, and Western sub-Saharan Africa and Oceania. Age-standardized incidence rates were high in Australasia and high-income North America, but low in Southeast Asia and South Asia. Age-standardized DALY rates were also numerically high in Australasia and high-income North America, and relatively low in Central, Eastern, Western, and Southern sub-Saharan Africa and Oceania. Fig. 2A and B show global DALY counts and rates by sex over time and across age groups, respectively. Both counts and rates were generally higher in men than in women, rising mainly from the 50s and peaking in the 70s. YLL rates declined at older ages, whereas the other measures remained similarly high. Death counts and age-standardized mortality rates followed patterns similar to those for DALYs. Supplement 3 (Figs. S12–S16) present regional percentage changes in age-standardized rates from 1990 to 2021, 2000 to 2010, and 2010 to 2021. From 1990 to 2021, age-standardized DALY rates generally increased substantially in Latin America and the Caribbean but decreased in Northern Africa and Central sub-Saharan Africa (Table 2).

Burden of motor neuron diseases by country in GBD 2021

Supplement 2 (Table S2) present country-level counts and age-standardized rates for MND prevalence, incidence, DALYs, YLDs, YLLs, and deaths in 2021. Age-standardized prevalence rates were particularly high in Ireland and Canada and lower in Somalia and the Central African Republic than in other countries. Age-standardized incidence rates were low in Malaysia and Indonesia but high in Ireland and the United Kingdom. Age-standardized DALYs were high in Finland and Ireland but low in Somalia and the Central African Republic. Within Latin America, French Guiana had significantly high prevalence, incidence, YLD, YLL, and mortality rates.

Disability-adjusted life years by Socio-demographic Index

Supplement 3 (Fig. S9_2) presents age-standardized prevalence, incidence, DALY, YLD, YLL, and mortality rates and their changes from 2000 to 2010 and from 2010 to 2021 by SDI quintile. In GBD 2021, age-standardized DALY rates per 100,000 people were significantly high in high-SDI regions such as Western Europe and Australasia, but considerably low in sub-Saharan Africa (Fig. 3). These rates were particularly high in high-SDI countries such as the United States and Finland. Incidence was lowest in low-middle-SDI regions; the other rates followed the order of low-, low-middle-, middle-, high-middle-, and high-SDI regions. In high-SDI regions, prevalence and YLD rates declined until 1995 and increased thereafter. DALY, YLL, and mortality rates in high-SDI regions peaked in 2012 (Figs. S18–S24 of Supplement 3).

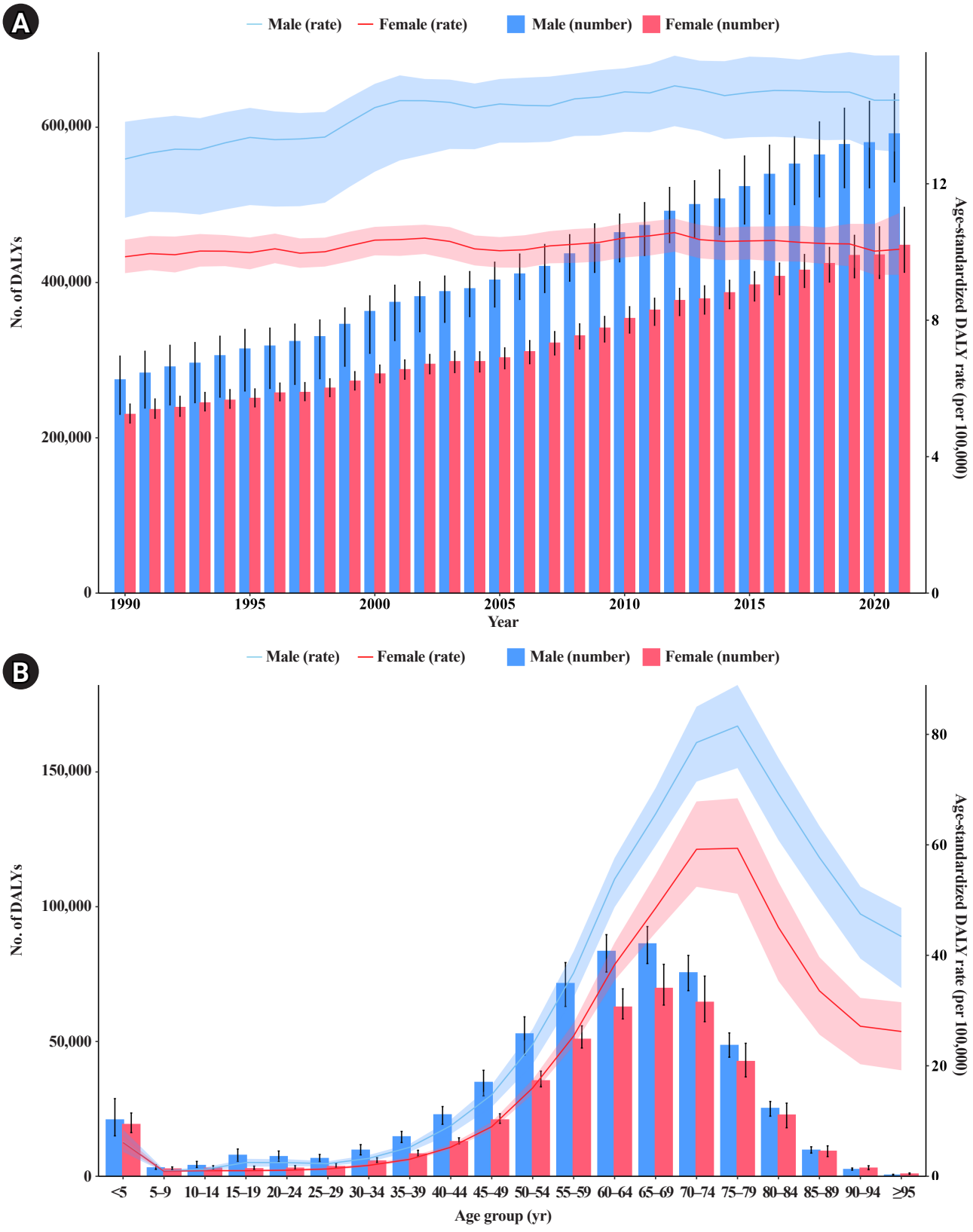


Fig. 2. (A) Disability-adjusted life year (DALY) counts and age-standardized DALY rates per 100,000 people by year and sex. DALY, disability-adjusted life year. (B) DALY counts and age-standardized DALY rates per 100,000 people by age group.

Table 2. Counts and age-standardized rates of prevalence, incidence, DALYs, YLDs, YLLs, and mortality for motor neuron diseases by GBD region in 1990 and 2021, and percentage changes in age-standardized rates from 1990 to 2021

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
Prevalence					
Global	161,926.07 (137,005.78 to 189,262.55)	3.36 (2.87 to 3.92)	272,732.25 (236,194.5 to 313,676.27)	3.31 (2.86 to 3.8)	−1.36 (−3.28 to 0.87)
Central Asia	1,755.59 (1,407.59 to 2,135.86)	2.56 (2.07 to 3.09)	2,374.94 (1,902.48 to 2,882.65)	2.49 (2.02 to 3.02)	−2.76 (−4.51 to −0.71)
Central Europe	4,511.81 (3,777.3 to 5,319.05)	3.56 (2.97 to 4.18)	5,063.36 (4,299.31 to 5,905.75)	4.00 (3.37 to 4.68)	12.35 (9.04 to 16.08)
Eastern Europe	7,712.76 (6,200.66 to 9,319.20)	3.44 (2.76 to 4.12)	7,587.71 (6,308.91 to 8,977.59)	3.58 (2.91 to 4.21)	3.87 (0.23 to 7.50)
Australasia	1,520.06 (1,314.86 to 1,743.66)	6.83 (5.95 to 7.80)	3,933.24 (3,379.46 to 4,535.55)	9.00 (7.78 to 10.12)	31.77 (24.31 to 40.06)
High-income Asia Pacific	8,352.38 (7,037.57 to 9,720.94)	4.45 (3.75 to 5.16)	14,361.01 (12,291.31 to 16,739.72)	5.05 (4.33 to 5.83)	13.67 (9.77 to 18.28)
High-income North America	25,479.85 (22,209.76 to 29,152.55)	8.13 (7.1 to 9.25)	47,430.54 (43,862.13 to 51,536.67)	9.23 (8.59 to 10.02)	13.59 (5.03 to 23.07)
Southern Latin America	1,888.64 (1,574.94 to 2,219.39)	3.86 (3.23 to 4.53)	3,706.52 (3,158.23 to 4,276.99)	5.00 (4.25 to 5.77)	29.61 (21.87 to 38.90)
Western Europe	37,571.6 (32,709.8 to 43,081.89)	7.74 (6.73 to 8.88)	67,562.67 (58,235.3 to 78,364.58)	9.66 (8.43 to 11.03)	24.69 (20.87 to 28.55)
Andean Latin America	605.13 (478.97 to 748.98)	1.70 (1.37 to 2.07)	1,228.55 (999.39 to 1,476.19)	1.87 (1.53 to 2.24)	9.89 (5.48 to 14.74)
Caribbean	862.87 (690.89 to 1041.49)	2.49 (2.02 to 2.97)	1,306.32 (1,100.2 to 1,527.24)	2.66 (2.24 to 3.12)	7.14 (2.59 to 12.42)
Central Latin America	3,603.83 (2,822.58 to 4,426.76)	2.25 (1.8 to 2.72)	6,311.84 (5,168.17 to 7,525.2)	2.46 (2.04 to 2.93)	9.59 (5.58 to 14.12)
Tropical Latin America	3,787.41 (2,999.25 to 4,644.3)	2.53 (2.03 to 3.04)	6,819.51 (5,688.40 to 7,989.78)	2.89 (2.40 to 3.39)	14.40 (9.72 to 19.35)
North Africa and Middle East	8,541.97 (6,908.81 to 10,298.74)	2.64 (2.16 to 3.15)	16,229.93 (13,098.91 to 19,540.16)	2.63 (2.15 to 3.14)	−0.41 (−2.54 to 1.74)
South Asia	16,033.69 (12,216.41 to 20,376.71)	1.49 (1.15 to 1.86)	29,895.69 (23,273.64 to 37,805.76)	1.58 (1.24 to 1.97)	6.02 (3.34 to 9.20)
East Asia	26,778.15 (21,281.79 to 33,189.21)	2.15 (1.74 to 2.62)	34,808.95 (28,296.16 to 42,072.18)	2.31 (1.85 to 2.81)	7.60 (2.70 to 13.92)

(Continued to the next page)

Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
Oceania	90.52 (71.34 to 113.57)	1.44 (1.16 to 1.75)	180.08 (140.43 to 224.66)	1.33 (1.07 to 1.64)	−7.27 (−10.10 to −3.94)
Southeast Asia	7,012.52 (5,447.87 to 8,777.4)	1.51 (1.2 to 1.87)	10,765.09 (8,470.95 to 13,330.79)	1.53 (1.21 to 1.89)	1.24 (−0.98 to 3.63)
Central Sub-Saharan Africa	557.54 (428.33 to 705.34)	1.17 (0.91 to 1.45)	1,380.53 (1,047.1 to 1,761.91)	1.11 (0.87 to 1.39)	−4.90 (−7.53 to −2.25)
Eastern Sub-Saharan Africa	2,105.77 (1,594.59 to 2,674.56)	1.27 (0.98 to 1.58)	4,807.08 (3,618 to 6,141.77)	1.23 (0.95 to 1.53)	−3.25 (−4.54 to −2.01)
Southern Sub-Saharan Africa	902.59 (693.55 to 1,131.42)	1.78 (1.39 to 2.21)	1,368.09 (1,061.68 to 1,728.99)	1.70 (1.33 to 2.11)	−4.67 (−6.36 to −2.48)
Western Sub-Saharan Africa	2251.41 (1,711.65 to 2,851.35)	1.31 (1.01 to 1.63)	5,610.62 (4,226.99 to 7,139.41)	1.26 (0.98 to 1.57)	−4.06 (−5.52 to −2.58)
Africa	8,834.68 (6,896.89 to 10,991.83)	1.54 (1.20 to 1.89)	18,601.43 (14,361.36 to 23,312)	1.44 (1.13 to 1.78)	−6.20 (−7.50 to −4.57)
African region	6,373.94 (4,894.06 to 7,996.95)	1.40 (1.09 to 1.73)	14,067.86 (10,671.8 to 17,825.8)	1.32 (1.03 to 1.64)	−5.59 (−6.64 to −4.22)
America	36,073.53 (31,424.79 to 41,338.72)	5.39 (4.68 to 6.18)	66,592.19 (60,691.38 to 73,159.26)	5.60 (5.09 to 6.18)	3.85 (−2.35 to 10)
Asia	64,900.43 (52,068.74 to 79,426.79)	2.13 (1.74 to 2.56)	103,790.47 (84,253.56 to 125,081.68)	2.19 (1.78 to 2.64)	2.49 (−0.05 to 5.51)
Central Africa	665.16 (510.78 to 841.90)	1.14 (0.88 to 1.42)	1,644.12 (1,251.41 to 2,104.27)	1.08 (0.84 to 1.34)	−5.49 (−7.83 to −3.44)
Commonwealth high income	11,568.23 (10,136.14 to 13,187.97)	8.75 (7.66 to 9.93)	23,231.41 (19,878.74 to 26,858.38)	10.65 (9.23 to 12.1)	21.71 (17.78 to 25.52)
Commonwealth low income	2,631.3 (2,043.24 to 3,325.34)	1.38 (1.09 to 1.70)	5,121.27 (3,948.10 to 6,422.49)	1.36 (1.08 to 1.69)	−1.07 (−3.59 to 1.78)
Commonwealth middle income	17,156.99 (13,041.25 to 21,808.77)	1.49 (1.15 to 1.86)	32,754.05 (25,421.51 to 41,517.23)	1.53 (1.21 to 1.92)	3.07 (0.74 to 5.67)
East Asia & Pacific–World Bank	43,482.36 (35,369.52 to 52,598.14)	2.39 (1.98 to 2.86)	63,684.96 (52,881.94 to 76,009.95)	2.48 (2.03 to 2.94)	3.56 (0.24 to 7.48)
Eastern Africa	2,009.47 (1,528.20 to 2,535.85)	1.30 (1.00 to 1.61)	4,537.30 (3,426.08 to 5,778.75)	1.26 (0.98 to 1.56)	−3.23 (−4.56 to −1.69)
Eastern Mediterranean region	7,766.69 (6,164.06 to 9,540.87)	2.15 (1.71 to 2.61)	15,676.76 (12,294.16 to 19,249.62)	2.09 (1.66 to 2.54)	−2.87 (−4.86 to −0.72)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
Europe	51,836.95 (45,108.23 to 59,778.31)	5.74 (4.98 to 6.61)	83,361.94 (72,590.68 to 96,071.27)	6.97 (6.07 to 7.98)	21.33 (17.80 to 24.87)
Europe & Central Asia–World Bank	53,023.05 (46,155.04 to 61,139.88)	5.62 (4.87 to 6.47)	85,087.70 (74,082.27 to 98,009.07)	6.74 (5.88 to 7.71)	19.93 (16.44 to 23.34)
European region	53,397.02 (46,481.30 to 61,567.85)	5.62 (4.87 to 6.46)	85,919.87 (74,822.05 to 98,960.43)	6.73 (5.87 to 7.70)	19.83 (16.32 to 23.22)
Latin America & Caribbean–World Bank	10,715.39 (8,515.99 to 12,955.31)	2.55 (2.07 to 3.05)	19,323.99 (16,183.25 to 22,654.92)	2.85 (2.39 to 3.34)	11.98 (7.51 to 16.88)
Middle East & North Africa–World Bank	6,373.15 (5,090.55 to 7,759.90)	2.63 (2.13 to 3.14)	12,217.42 (9,769.99 to 14,803.07)	2.58 (2.10 to 3.10)	−1.60 (−3.51 to 0.41)
North America	25,478.10 (22,207.95 to 29,150.68)	8.13 (7.10 to 9.25)	47,428.45 (43,860.30 to 51,534.17)	9.23 (8.58 to 10.02)	13.59 (5.03 to 23.07)
Northern Africa	2,721.15 (2,171.35 to 3,336.37)	2.31 (1.88 to 2.80)	4,789.73 (3,817.19 to 5,835.38)	2.28 (1.84 to 2.77)	−1.29 (−3.89 to 1.58)
Region of the Americas	36,073.53 (31,424.79 to 41,338.72)	5.39 (4.68 to 6.18)	66,592.19 (60,691.38 to 73,159.26)	5.60 (5.09 to 6.18)	3.85 (−2.35 to 10.00)
South Asia–World Bank	16,494.14 (12,575.46 to 20,948.56)	1.49 (1.16 to 1.87)	30,841.33 (24,061.73 to 38,920.24)	1.58 (1.25 to 1.97)	6.02 (3.43 to 9.09)
South-East Asia region	19,194.47 (14,669.19 to 24,348.66)	1.49 (1.16 to 1.85)	32,960.20 (25,804.18 to 41,513.77)	1.56 (1.24 to 1.94)	4.81 (2.47 to 7.41)
Southern Africa	1,393.02 (1,077.19 to 1,745.96)	1.61 (1.26 to 1.99)	2,611.28 (2,010.46 to 3,285.70)	1.50 (1.17 to 1.87)	−6.32 (−7.77 to −4.39)
Sub-Saharan Africa–World Bank	6,137.43 (4,673.92 to 7,732.62)	1.34 (1.04 to 1.67)	13,857.74 (10,483.87 to 17,608.96)	1.28 (0.99 to 1.59)	−5.06 (−6.11 to −3.68)
Western Africa	2,045.89 (1,553.72 to 2,596.47)	1.32 (1.01 to 1.64)	5,019.00 (3,778.63 to 6,387.10)	1.26 (0.98 to 1.58)	−4.00 (−5.36 to −2.42)
Western Pacific region	38,270.39 (31,250.08 to 46,178.20)	2.53 (2.11 to 3.03)	56,289.41 (46,937.50 to 66,980.31)	2.66 (2.19 to 3.16)	5.12 (1.35 to 9.52)
World Bank high income	78,739.13 (68,312.74 to 90,435.45)	6.71 (5.87 to 7.66)	141,970.45 (125,872.21 to 160,342.78)	7.90 (7.06 to 8.81)	17.66 (13.52 to 22.22)
World Bank low income	4,046.31 (3,198.77 to 5,005.81)	1.48 (1.17 to 1.81)	8,655.81 (6,713.71 to 10,845.69)	1.38 (1.08 to 1.69)	−6.81 (−8.15 to −5.31)
World Bank lower middle income	31,505.54 (24,269.03 to 39,461.96)	1.62 (1.27 to 2.01)	55,840.07 (43,925.42 to 69,782.02)	1.62 (1.28 to 2.00)	−0.23 (−2.26 to 2.05)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
World Bank upper middle income	47,479.48 (38,424.91 to 57,689.39)	2.37 (1.93 to 2.83)	66,044.63 (54,179.12 to 78,428.62)	2.52 (2.04 to 3.02)	6.32 (3.17 to 10.25)
Incidence					
Global	36,769.25 (33,067.78 to 41,299.83)	0.81 (0.72 to 0.90)	64,177.73 (58,506.16 to 70,270.30)	0.77 (0.70 to 0.84)	−4.69 (−6.53 to −2.86)
Central Asia	298.75 (247.86 to 357.21)	0.48 (0.39 to 0.59)	410.93 (338.87 to 503.34)	0.44 (0.36 to 0.53)	−8.09 (−10.35 to −6.15)
Central Europe	853.95 (735.84 to 983.85)	0.67 (0.58 to 0.76)	1,164.10 (1,046.26 to 1,280.75)	0.75 (0.67 to 0.82)	11.99 (7.46 to 16.96)
Eastern Europe	1,318.60 (1,096.92 to 1,578.02)	0.56 (0.47 to 0.67)	1,726.53 (1,520.87 to 1,936.90)	0.66 (0.57 to 0.73)	17.48 (9.20 to 25.11)
Australasia	477.77 (453.09 to 502.23)	2.11 (2.00 to 2.22)	1,274.47 (1,224.52 to 1,329.11)	2.60 (2.49 to 2.72)	23.23 (19.81 to 26.74)
High-income Asia Pacific	1,644.71 (1,469.82 to 1,808.26)	0.88 (0.79 to 0.96)	3,268.31 (3,041.88 to 3,491.13)	0.91 (0.84 to 0.99)	4.15 (2.04 to 6.95)
High-income North America	5,926.27 (5,606.01 to 6,287.52)	1.82 (1.71 to 1.93)	12,656.59 (12,143.54 to 13,195.28)	2.10 (2.02 to 2.19)	15.51 (12.02 to 19.37)
Southern Latin America	380.88 (330.61 to 431.43)	0.80 (0.69 to 0.90)	815.08 (753.94 to 881.01)	1.05 (0.96 to 1.13)	31.30 (21.03 to 42.52)
Western Europe	8298.92 (7795.58 to 8819.91)	1.64 (1.54 to 1.75)	15,472.08 (14,696.82 to 16,253.81)	2.00 (1.90 to 2.12)	21.86 (19.46 to 24.34)
Andean Latin America	127.83 (107.62 to 148.78)	0.43 (0.36 to 0.50)	305.23 (265.27 to 343.1)	0.49 (0.43 to 0.55)	15.03 (7.92 to 22.96)
Caribbean	182.16 (155.20 to 207.39)	0.59 (0.50 to 0.67)	376.67 (340.24 to 411.87)	0.75 (0.68 to 0.82)	27.25 (19.04 to 36.82)
Central Latin America	697.39 (597.33 to 806.51)	0.51 (0.44 to 0.59)	1,575.25 (1,392.61 to 1,746.00)	0.63 (0.56 to 0.70)	23.41 (16.18 to 31.66)
Tropical Latin America	803.50 (691.73 to 915.90)	0.65 (0.56 to 0.74)	2,113.50 (1,920.63 to 2,293.72)	0.86 (0.79 to 0.93)	32.58 (24.94 to 41.49)
North Africa and Middle East	1,687.14 (1,447.14 to 1,940.02)	0.57 (0.48 to 0.67)	3,110.80 (2,644.63 to 3,631.76)	0.55 (0.47 to 0.63)	−3.29 (−6.42 to −0.55)
South Asia	3,754.41 (3,086.41 to 4,607.41)	0.40 (0.32 to 0.49)	6,310.71 (5,187.62 to 7,623.12)	0.37 (0.31 to 0.44)	−6.84 (−11.88 to −3.36)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
East Asia	7,088.61 (6,127.17 to 8,224.44)	0.65 (0.57 to 0.75)	7,700.10 (6,320.39 to 9,120.27)	0.47 (0.40 to 0.54)	−28.27 (−31.72 to −24.00)
Oceania	23.09 (19.36 to 27.10)	0.44 (0.37 to 0.52)	46.81 (38.89 to 55.26)	0.39 (0.32 to 0.46)	−12.00 (−14.15 to −9.88)
Southeast Asia	1,531.75 (1,261.74 to 1,839.53)	0.40 (0.33 to 0.48)	2,380.55 (1,949.12 to 2,904.51)	0.35 (0.29 to 0.42)	−12.29 (−14.74 to −9.90)
Central Sub-Saharan Africa	175.03 (143.49 to 211.64)	0.45 (0.36 to 0.56)	412.58 (336.87 to 500.07)	0.42 (0.34 to 0.52)	−5.86 (−8.46 to −3.15)
Eastern Sub-Saharan Africa	659.85 (540.43 to 805.21)	0.50 (0.40 to 0.63)	1,323.97 (1,078.67 to 1,640.5)	0.44 (0.35 to 0.56)	−12.25 (−13.49 to −11.13)
Southern Sub-Saharan Africa	188.75 (155.41 to 231.04)	0.45 (0.37 to 0.57)	289.63 (233.5 to 358.91)	0.40 (0.33 to 0.50)	−11.40 (−12.81 to −9.76)
Western Sub-Saharan Africa	649.91 (541.33 to 779.34)	0.44 (0.36 to 0.54)	1,443.85 (1,203.82 to 1,732.06)	0.39 (0.32 to 0.47)	−10.08 (−11.6 to −8.61)
Africa	2,280.34 (1,895.60 to 2,728.69)	0.46 (0.38 to 0.58)	4,505.35 (3724.08 to 5446.59)	0.41 (0.34 to 0.51)	−11.08 (−12.80 to −9.75)
African region	1,747.55 (1,450.20 to 2,105.33)	0.46 (0.37 to 0.57)	3,582.50 (2,951.93 to 4,357.92)	0.41 (0.33 to 0.51)	−10.91 (−12.23 to −9.74)
America	8,089.38 (7,504.18 to 8,719.41)	1.26 (1.18 to 1.36)	17,781.34 (16,869.71 to 18,685.03)	1.40 (1.33 to 1.48)	10.61 (7.49 to 13.71)
Asia	15,462.51 (13,357.02 to 18,059.19)	0.56 (0.48 to 0.65)	22,711.92 (19,411.40 to 26,490.45)	0.48 (0.41 to 0.55)	−14.85 (−16.66 to −12.85)
Central Africa	210.27 (172.95 to 252.41)	0.43 (0.35 to 0.54)	492.65 (404.04 to 595.14)	0.41 (0.33 to 0.50)	−5.34 (−7.58 to −3.05)
Commonwealth high income	2,810.02 (2,665.67 to 2,968.50)	2.02 (1.91 to 2.14)	6,057.69 (5,764.92 to 6,349.05)	2.48 (2.36 to 2.61)	22.51 (20.21 to 24.70)
Commonwealth low income	679.18 (559.99 to 822.73)	0.43 (0.34 to 0.53)	1,209.93 (988.69 to 1,468.64)	0.37 (0.30 to 0.46)	−12.03 (−14.87 to −9.96)
Commonwealth middle income	4,017.42 (3,301.67 to 4,920.64)	0.40 (0.33 to 0.49)	6,978.39 (5,726.09 to 8,417.6)	0.36 (0.30 to 0.44)	−8.40 (−12.71 to −5.18)
East Asia & Pacific–World Bank	10,713.72 (9,407.20 to 12,275.52)	0.66 (0.58 to 0.75)	14,591.13 (12,654.4 to 16,691.46)	0.53 (0.46 to 0.6)	−20.03 (−21.83 to −17.31)
Eastern Africa	608.81 (499.89 to 737.60)	0.48 (0.38 to 0.61)	1,206.79 (985.42 to 1,487.17)	0.42 (0.34 to 0.54)	−11.99 (−13.38 to −10.76)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
Eastern Mediterranean region	1602.99 (1340.36 to 1894.46)	0.49 (0.4 to 0.59)	2,979.5 (2,457.99 to 3,554.74)	0.44 (0.37 to 0.53)	−9.34 (−12.71 to −6.84)
Europe	10,882.38 (10,068.60 to 11,723.34)	1.17 (1.08 to 1.26)	19,078.07 (17,992.21 to 20,111.73)	1.43 (1.35 to 1.53)	22.97 (19.82 to 26.14)
Europe & Central Asia–World Bank	11,086.84 (10,239.27 to 11,974.81)	1.14 (1.05 to 1.24)	19,374.79 (18,257.57 to 20,470.29)	1.39 (1.31 to 1.48)	21.75 (18.67 to 24.90)
European region	11,161.57 (10,307.25 to 12,055.24)	1.14 (1.05 to 1.23)	19,541.74 (18,413.66 to 20,651.9)	1.38 (1.30 to 1.48)	21.56 (18.50 to 24.69)
Latin America & Caribbean–World Bank	2,184.93 (1,879.53 to 2,491.23)	0.60 (0.52 to 0.69)	5,171.69 (4,667.53 to 5,650.14)	0.76 (0.69 to 0.83)	25.43 (18.03 to 33.93)
Middle East & North Africa–World Bank	1,182.49 (999.23 to 1,384.26)	0.54 (0.45 to 0.64)	2,140.03 (1,777.88 to 2,551.72)	0.49 (0.42 to 0.58)	−8.47 (−11.60 to −6.06)
North America	5,926.07 (5,605.86 to 6,287.26)	1.82 (1.71 to 1.93)	12,656.63 (12,143.66 to 13,195.30)	2.10 (2.02 to 2.19)	15.51 (12.02 to 19.37)
Northern Africa	525.11 (439.15 to 620.72)	0.49 (0.41 to 0.6)	889.11 (736.01 to 1,057.28)	0.45 (0.37 to 0.53)	−9.31 (−12.85 to −6.33)
Region of the Americas	8,089.38 (7,504.18 to 8,719.41)	1.26 (1.18 to 1.36)	17,781.34 (16,869.71 to 18,685.03)	1.40 (1.33 to 1.48)	10.61 (7.49 to 13.71)
South Asia–World Bank	3870.60 (3,184.66 to 4,744.52)	0.40 (0.33 to 0.49)	6,552.16 (5,394.60 to 7,890.74)	0.37 (0.31 to 0.44)	−6.40 (−11.35 to −2.95)
South-East Asia region	4,464.60 (3,680.65 to 5,462.32)	0.40 (0.33 to 0.49)	7,156.57 (5,860.12 to 8,706.37)	0.36 (0.30 to 0.44)	−8.45 (−12.55 to −5.49)
Southern Africa	346.41 (286.33 to 422.98)	0.49 (0.39 to 0.62)	626.94 (510.05 to 769.43)	0.43 (0.35 to 0.53)	−11.85 (−13.37 to −10.54)
Sub-Saharan Africa–World Bank	1,761.19 (1,459.67 to 2,120.49)	0.46 (0.37 to 0.58)	3,625.88 (2,990.57 to 4,408.13)	0.41 (0.33 to 0.51)	−10.61 (−11.88 to −9.46)
Western Africa	589.75 (491.63 to 707.16)	0.44 (0.36 to 0.54)	1,289.87 (1,076.11 to 1,548.21)	0.39 (0.33 to 0.47)	−10.21 (−11.86 to −8.71)
Western Pacific region	9,555.30 (8,420.88 to 10,891.18)	0.71 (0.62 to 0.80)	12,835.80 (11,198.34 to 14,542.77)	0.56 (0.49 to 0.63)	−21.27 (−23.32 to −18.21)
World Bank high income	17,410.54 (16,346.90 to 18,547.83)	1.44 (1.35 to 1.54)	34,567.74 (32,860.75 to 36,206.25)	1.68 (1.60 to 1.76)	16.29 (13.97 to 19.03)
World Bank low income	1,252.71 (1,049.85 to 1,486.01)	0.53 (0.43 to 0.65)	2,462.48 (2,044.49 to 2,952.61)	0.48 (0.39 to 0.58)	−9.39 (−10.52 to −8.10)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
World Bank lower middle income	7,089.59 (5,858.02 to 8,573.06)	0.41 (0.34 to 0.51)	11,823.22 (9,777.40 to 14,267.43)	0.37 (0.31 to 0.45)	−9.53 (−12.91 to −6.82)
World Bank upper middle income	10,984.41 (9,506.66 to 12,739.65)	0.61 (0.53 to 0.71)	15,271.14 (13,175.08 to 17,519.43)	0.54 (0.46 to 0.61)	−12.24 (−14.79 to −9.00)
DALYs					
Global	506,146.42 (462,034.99 to 545,049.77)	11.22 (10.39 to 11.98)	1,040,565.98 (963,064.26 to 1,123,956.29)	12.17 (11.24 to 13.15)	8.42 (−0.78 to 18.64)
Central Asia	572.26 (430.87 to 745.26)	0.82 (0.62 to 1.05)	1,491.59 (1,283.82 to 1,745.33)	1.56 (1.35 to 1.82)	91.23 (55.58 to 138.25)
Central Europe	13,398.18 (12,873.50 to 14,034.02)	11.09 (10.64 to 11.63)	32,148.46 (29,468.16 to 35,149.74)	19.82 (18.27 to 21.71)	78.71 (63.03 to 96.26)
Eastern Europe	10,039.01 (7,604.27 to 12,851.58)	4.16 (3.20 to 5.31)	64,275.53 (59,370.93 to 69,493.62)	21.06 (19.54 to 22.69)	406.39 (289.41 to 576.09)
Australasia	10,280.94 (9,851.36 to 10,701.05)	46.81 (44.95 to 48.65)	22,757.76 (20,520.39 to 24,987.42)	49.54 (45.12 to 54.17)	5.83 (−3.18 to 16.34)
High-income Asia Pacific	31,936.40 (30,421.59 to 33,170.79)	16.35 (15.46 to 17.01)	68,294.82 (61,565.92 to 73,931.76)	18.11 (16.76 to 19.47)	10.78 (4.57 to 18.60)
High-income North America	123,874 (119,504.16 to 127,252.34)	39.82 (38.60 to 40.85)	237,211.58 (224,878.68 to 247,050.97)	41.58 (39.69 to 43.26)	4.44 (0.60 to 8.08)
Southern Latin America	1,542.72 (1,417.19 to 1,687.68)	3.21 (2.96 to 3.51)	18,154.21 (16,602.27 to 19,791.95)	22.7 (20.73 to 24.72)	606.72 (527.74 to 700.43)
Western Europe	179,754.93 (174,002.21 to 183,650.46)	38.34 (37.36 to 39.13)	305,400.11 (278,825.27 to 334,427.62)	41.57 (38.30 to 45.31)	8.44 (0.17 to 17.69)
Andean Latin America	161.48 (116.05 to 224.68)	0.49 (0.36 to 0.67)	4,963.05 (3,822.64 to 6,019.39)	8.00 (6.17 to 9.71)	1,524.93 (955.98 to 2,265.76)
Caribbean	304.68 (244.59 to 382.69)	0.92 (0.74 to 1.13)	6,637.11 (5,610.79 to 7,755.56)	12.75 (10.76 to 14.89)	1,287.23 (983.11 to 1,706.63)
Central Latin America	8,504.22 (8,163.32 to 8,891.82)	6.76 (6.55 to 7.00)	35,995.34 (31,563.75 to 40,871.48)	13.92 (12.20 to 15.83)	105.88 (79.28 to 133.65)
Tropical Latin America	13,175.86 (12,688.37 to 13,824.77)	10.87 (10.50 to 11.31)	56,816.30 (53,278.94 to 60,714.17)	22.24 (20.86 to 23.76)	104.65 (87.27 to 118.29)
North Africa and Middle East	13,111.47 (8,420.76 to 21,978.26)	3.57 (2.33 to 5.66)	28,916.62 (21,767.86 to 38,490.68)	5.27 (3.93 to 7.02)	47.63 (−12.12 to 144.70)
South Asia	4,800.63 (3,429.16 to 6,567.80)	0.47 (0.33 to 0.67)	18,449.55 (12,113.21 to 24,784.22)	1.08 (0.69 to 1.45)	127.54 (73.46 to 223.55)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
East Asia	90,417.69 (52,777.60 to 114,962.79)	7.96 (4.73 to 10.09)	128,689.12 (86,938.50 to 173,235.30)	7.73 (5.03 to 10.02)	−2.95 (−41.21 to 75.89)
Oceania	26.23 (19.39 to 34.56)	0.46 (0.35 to 0.59)	47.43 (34.84 to 63.90)	0.37 (0.28 to 0.50)	−19.31 (−28.35 to −6.64)
Southeast Asia	2,543.41 (1,871.77 to 3,284.60)	0.61 (0.44 to 0.80)	6,738.84 (4,964.22 to 8,644.26)	0.95 (0.70 to 1.21)	54.6 (20.10 to 95.72)
Central Sub-Saharan Africa	153.40 (110.75 to 212.27)	0.31 (0.22 to 0.42)	316.06 (211.32 to 455.64)	0.26 (0.18 to 0.36)	−16.48 (−24.45 to −7.45)
Eastern Sub-Saharan Africa	521.59 (368.24 to 733.51)	0.30 (0.22 to 0.42)	1,070.88 (694.99 to 1,555.15)	0.28 (0.19 to 0.39)	−9.45 (−13.98 to −5.16)
Southern Sub-Saharan Africa	423.11 (265.74 to 671.05)	0.89 (0.53 to 1.40)	557.12 (345.85 to 803.46)	0.68 (0.44 to 0.97)	−23.75 (−46.46 to 15.35)
Western Sub-Saharan Africa	604.22 (437.31 to 826.73)	0.34 (0.25 to 0.45)	1,634.51 (1,202.51 to 2,205.01)	0.37 (0.28 to 0.49)	9.15 (1.01 to 21.72)
Africa	2,676.07 (1,998.34 to 3,519.97)	0.45 (0.34 to 0.59)	5,171.83 (3,795.45 to 7,080.42)	0.42 (0.32 to 0.57)	−5.80 (−13.00 to 6.75)
African region	1,841.55 (1,341.32 to 2,505.62)	0.41 (0.30 to 0.54)	4,156.49 (3,104.61 to 5,646.22)	0.42 (0.32 to 0.56)	4.10 (−5.38 to 16.82)
America	147,492.20 (142,781.03 to 151,409.28)	23.08 (22.34 to 23.69)	358,497.33 (339,730.12 to 376,883.31)	28.25 (26.76 to 29.69)	22.39 (16.90 to 28.55)
Asia	143,029.69 (102,839.52 to 169,391.83)	5.18 (3.89 to 6.05)	252,770.72 (201,243.16 to 301,064)	5.12 (4.06 to 6.04)	−1.29 (−23.29 to 33.49)
Central Africa	184.18 (136.19 to 251.41)	0.30 (0.22 to 0.41)	410.88 (287.72 to 573.13)	0.27 (0.19 to 0.37)	−10.27 (−18.18 to −1.08)
Commonwealth high income	57,309.39 (55,850.94 to 58,628.71)	43.21 (42.19 to 44.18)	107,221.95 (100,036.84 to 114,281.92)	46.62 (43.82 to 49.52)	7.89 (2.50 to 14.54)
Commonwealth low income	682.79 (495.56 to 933.70)	0.35 (0.25 to 0.48)	1,848.68 (1,171.43 to 2,649.60)	0.55 (0.33 to 0.82)	55.28 (15.28 to 108)
Commonwealth middle income	5,384.37 (3,911.99 to 7,148.67)	0.50 (0.36 to 0.68)	20,701.93 (14,316.67 to 27,057.19)	1.09 (0.74 to 1.43)	118.99 (73.13 to 204.55)
East Asia & Pacific–World Bank	135,157.27 (96,346.56 to 160,221.39)	8.18 (6.03 to 9.59)	225,528.84 (179,885.17 to 271,918.67)	7.75 (6.03 to 9.31)	−5.26 (−29.69 to 34.75)
Eastern Africa	502.87 (353.88 to 706.58)	0.32 (0.23 to 0.44)	1,376.92 (1,025.7 to 1,835.79)	0.48 (0.39 to 0.60)	46.71 (32.38 to 69.40)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
Eastern Mediterranean region	2,755.97 (2,110.36 to 3,532.60)	0.74 (0.57 to 0.96)	7,753.33 (6,269.99 to 9,668.84)	1.17 (0.95 to 1.43)	57.14 (36.45 to 92.35)
Europe	212,503.73 (203,833.69 to 224,394.46)	23.74 (22.67 to 25.56)	422,075.93 (390,517.62 to 456,792.65)	33.06 (30.76 to 35.81)	39.24 (28.01 to 53.73)
Europe & Central Asia–World Bank	212,500.69 (203,822.81 to 224,421.34)	22.52 (21.51 to 24.17)	422,360.76 (390,754.03 to 457,074.94)	31.07 (28.90 to 33.63)	37.97 (26.87 to 52.14)
European region	214,049.05 (205,331.26 to 225,996.67)	22.52 (21.52 to 24.16)	425,656.02 (393,759.59 to 460,610.58)	30.95 (28.79 to 33.50)	37.46 (26.45 to 51.51)
Latin America & Caribbean–World Bank	23,677.27 (22,739.37 to 24,767.79)	6.61 (6.39 to 6.85)	122,325.17 (112,710.72 to 132,838.82)	17.32 (15.94 to 18.82)	162.1 (139.97 to 186.5)
Middle East & North Africa–World Bank	3,640.47 (3,145.77 to 4,270.13)	1.78 (1.57 to 2.03)	8,516.23 (7,448.83 to 9,768.75)	2.12 (1.89 to 2.4)	19.11 (9.02 to 33.09)
North America	123,867.47 (119,497.52 to 127,245.72)	39.81 (38.6 to 40.85)	237,215.5 (224,881.02 to 247,053.13)	41.58 (39.69 to 43.26)	4.44 (0.6 to 8.09)
Northern Africa	893.21 (686.49 to 1182.03)	0.71 (0.54 to 0.91)	1,086.62 (737.82 to 1,533.3)	0.52 (0.36 to 0.73)	−26.29 (−37.05 to −9.61)
Region of the Americas	147,492.2 (142,781.03 to 151,409.28)	23.08 (22.34 to 23.69)	358,497.33 (339,730.12 to 376,883.31)	28.25 (26.76 to 29.69)	22.39 (16.9 to 28.55)
South Asia–World Bank	4,955.46 (3,540.44 to 6,756.84)	0.48 (0.34 to 0.67)	19,314.53 (12,670.69 to 25,887.5)	1.1 (0.7 to 1.47)	130.02 (74.66 to 224.55)
South-East Asia region	6,645.58 (4,845.13 to 8,916.88)	0.55 (0.39 to 0.77)	21,162.98 (14,203.09 to 28,284.52)	1.06 (0.7 to 1.42)	91.72 (51.02 to 162.79)
Southern Africa	548.34 (371.07 to 793.38)	0.67 (0.44 to 0.96)	836.82 (551.69 to 1,178.67)	0.49 (0.33 to 0.69)	−26.32 (−44.95 to 3.98)
Sub-Saharan Africa–World Bank	1,789.35 (1,304.45 to 2,432.47)	0.39 (0.29 to 0.52)	4,098.63 (3,061.06 to 5,569.88)	0.41 (0.31 to 0.54)	4.66 (−5.05 to 17.36)
Western Africa	547.48 (394.49 to 750.70)	0.34 (0.25 to 0.46)	1,460.59 (1,074.17 to 1,967.99)	0.37 (0.27 to 0.49)	9.41 (1.15 to 22.61)
Western Pacific region	130,918.40 (92,779.70 to 155,560.2)	9.51 (6.95 to 11.18)	216,168.10 (171,223.97 to 262,325.51)	9.00 (6.90 to 10.87)	−5.41 (−31.31 to 36.71)
World Bank high income	361,573.92 (351,537.96 to 369,561.04)	31.91 (31.10 to 32.59)	683,227.25 (635,035.00 to 732,604.69)	35.27 (33.10 to 37.59)	10.52 (4.42 to 17.02)
World Bank low income	1,768.38 (1,273.72 to 2,447.55)	0.61 (0.43 to 0.83)	2,853.71 (2,022.97 to 4,117.85)	0.48 (0.34 to 0.71)	−20.18 (−38.82 to 3.43)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
World Bank lower middle income	12,431.33 (9,513.74 to 16,046.75)	0.72 (0.55 to 0.95)	35,536.73 (26,864.80 to 44,615.46)	1.17 (0.89 to 1.47)	61.29 (29.93 to 107.75)
World Bank upper middle income	129,775.04 (88,809.21 to 162,041.63)	6.67 (4.64 to 8.27)	317,645.82 (267,020.27 to 369,680.48)	10.17 (8.42 to 11.79)	52.44 (12.03 to 119.15)
YLDs					
Global	34,425.85 (23,884.86 to 47,211.93)	0.71 (0.50 to 0.97)	57,889.10 (40,686.61 to 78,030.59)	0.70 (0.49 to 0.96)	−1.49 (−3.45 to 0.70)
Central Asia	373.43 (252.39 to 531.08)	0.54 (0.37 to 0.76)	505.22 (337.08 to 714.30)	0.53 (0.36 to 0.75)	−2.75 (−4.51 to −0.71)
Central Europe	959.60 (643.24 to 1323.02)	0.76 (0.51 to 1.05)	1,076.31 (738.23 to 1,442.31)	0.85 (0.58 to 1.17)	12.33 (9.04 to 16.08)
Eastern Europe	1,640.38 (1,097.12 to 2,274.79)	0.73 (0.49 to 1.03)	1,613.03 (1,105.47 to 2,175.16)	0.76 (0.52 to 1.06)	3.84 (0.23 to 7.50)
Australasia	323.02 (229.48 to 434.08)	1.45 (1.03 to 1.95)	834.67 (595.88 to 1,125.01)	1.91 (1.36 to 2.56)	31.65 (24.17 to 39.84)
High-income Asia Pacific	1,775.42 (1,239.49 to 2,387.67)	0.94 (0.66 to 1.28)	3,050.66 (2,143.82 to 4,107.10)	1.07 (0.75 to 1.47)	13.66 (9.77 to 18.28)
High-income North America	5,414.57 (3,851.80 to 7,341.58)	1.73 (1.23 to 2.32)	10,067.48 (7,305.14 to 13,261.06)	1.96 (1.42 to 2.59)	13.49 (4.93 to 22.96)
Southern Latin America	401.60 (269.65 to 550.46)	0.82 (0.55 to 1.12)	787.67 (547.58 to 1,056.42)	1.06 (0.74 to 1.43)	29.55 (21.87 to 38.9)
Western Europe	7,979.49 (5,690.76 to 10,789)	1.65 (1.16 to 2.24)	14,277.5 (10,182.51 to 19,057.92)	2.05 (1.47 to 2.74)	24.29 (20.63 to 28.09)
Andean Latin America	128.70 (85.98 to 186.73)	0.36 (0.25 to 0.51)	261.24 (177.99 to 368.47)	0.40 (0.27 to 0.56)	9.87 (5.48 to 14.74)
Caribbean	183.49 (125.38 to 260.12)	0.53 (0.36 to 0.74)	277.69 (193.15 to 378.36)	0.57 (0.39 to 0.78)	7.12 (2.59 to 12.42)
Central Latin America	766.49 (514.22 to 1,090.77)	0.48 (0.33 to 0.67)	1342.02 (922.43 to 1871.34)	0.52 (0.36 to 0.73)	9.55 (5.58 to 14.12)
Tropical Latin America	805.67 (538.85 to 1149.23)	0.54 (0.36 to 0.75)	1,449.77 (993.23 to 1,990.56)	0.61 (0.42 to 0.85)	14.35 (9.72 to 19.35)
North Africa and Middle East	1817.12 (1229.26 to 2592.27)	0.56 (0.38 to 0.78)	3,452.41 (2314.95 to 4,837.32)	0.56 (0.38 to 0.78)	−0.42 (−2.54 to 1.74)
South Asia	3,411.10 (2,155.44 to 4,981.31)	0.32 (0.21 to 0.45)	6,360.46 (4,134.12 to 9,175.24)	0.34 (0.22 to 0.48)	6.02 (3.34 to 9.20)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
East Asia	5,697.36 (3,738.23 to 8,077.29)	0.46 (0.30 to 0.64)	7,403.74 (4,983.73 to 10,221.69)	0.49 (0.33 to 0.70)	7.60 (2.70 to 13.92)
Oceania	19.25 (12.79 to 27.34)	0.31 (0.21 to 0.43)	38.31 (25.31 to 55.16)	0.28 (0.19 to 0.40)	−7.26 (−10.10 to −3.94)
Southeast Asia	1,491.65 (976.79 to 2,167.92)	0.32 (0.21 to 0.46)	2,289.86 (1,487.07 to 3,271.89)	0.33 (0.21 to 0.47)	1.24 (−0.98 to 3.63)
Central Sub-Saharan Africa	118.60 (77.18 to 173.31)	0.25 (0.16 to 0.35)	293.67 (190.55 to 426.45)	0.24 (0.16 to 0.34)	−4.91 (−7.53 to −2.25)
Eastern Sub-Saharan Africa	447.96 (288.58 to 655.71)	0.27 (0.18 to 0.39)	1,022.71 (654.76 to 1,498.95)	0.26 (0.17 to 0.37)	−3.24 (−4.54 to −2.01)
Southern Sub-Saharan Africa	191.99 (125.33 to 278.82)	0.38 (0.25 to 0.54)	291.03 (191.32 to 420.45)	0.36 (0.24 to 0.52)	−4.67 (−6.36 to −2.48)
Western Sub-Saharan Africa	478.96 (308.71 to 698.37)	0.28 (0.18 to 0.40)	1,193.65 (759.63 to 1,743.71)	0.27 (0.18 to 0.38)	−4.05 (−5.52 to −2.58)
Africa	1,879.32 (1,237.56 to 2,702.53)	0.33 (0.22 to 0.46)	3,957.32 (2,584.74 to 5,705.97)	0.31 (0.20 to 0.44)	−6.19 (−7.50 to −4.57)
African region	1,355.91 (881.67 to 1,967.64)	0.30 (0.20 to 0.42)	2,992.85 (1,922.6 to 4,360.39)	0.28 (0.18 to 0.40)	−5.58 (−6.64 to −4.22)
America	7,667.74 (5,404.07 to 10,339.44)	1.15 (0.81 to 1.54)	14,141.02 (10,138.65 to 18,782.62)	1.19 (0.86 to 1.59)	3.77 (−2.40 to 9.91)
Asia	13,805.45 (9,133.88 to 19,495.70)	0.45 (0.30 to 0.63)	22,072.20 (14,839.01 to 30,703.82)	0.47 (0.31 to 0.65)	2.48 (−0.06 to 5.50)
Central Africa	141.49 (92.04 to 206.89)	0.24 (0.16 to 0.35)	349.75 (226.77 to 508.64)	0.23 (0.15 to 0.33)	−5.49 (−7.83 to −3.44)
Commonwealth high income	2,457.08 (1,755.42 to 3,341.18)	1.86 (1.33 to 2.50)	4,896.87 (3,513.81 to 6,577.7)	2.25 (1.61 to 3.03)	21.06 (17.20 to 24.9)
Commonwealth low income	559.69 (366.71 to 813.85)	0.29 (0.19 to 0.42)	1,089.49 (712.54 to 1,577.02)	0.29 (0.19 to 0.41)	−1.06 (−3.59 to 1.78)
Commonwealth middle income	3,650.1 (2,304.31 to 5,342.74)	0.32 (0.21 to 0.45)	6,968.58 (4,525.61 to 10,089.18)	0.33 (0.21 to 0.47)	3.07 (0.74 to 5.67)
East Asia & Pacific–World Bank	9,249.02 (6,189.27 to 13,008.93)	0.51 (0.34 to 0.70)	13,539.96 (9,322.87 to 18,504.23)	0.53 (0.36 to 0.74)	3.55 (0.24 to 7.47)
Eastern Africa	427.47 (275.52 to 623.26)	0.28 (0.18 to 0.40)	965.34 (615.49 to 1,409.92)	0.27 (0.18 to 0.38)	−3.22 (−4.56 to −1.69)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
Eastern Mediterranean region	1,652.21 (1,105.59 to 2,363.66)	0.46 (0.30 to 0.65)	3,335.17 (2,209.15 to 4,797.28)	0.44 (0.29 to 0.63)	−2.87 (−4.86 to −0.72)
Europe	11,013.71 (7,819.57 to 14,862.50)	1.22 (0.86 to 1.65)	17,636.54 (12,575.11 to 23,634.31)	1.48 (1.06 to 2.00)	21.00 (17.50 to 24.40)
Europe & Central Asia–World Bank	11,266.01 (7,983.23 to 15,197.26)	1.19 (0.84 to 1.62)	18,003.68 (12,851.53 to 24,053.14)	1.43 (1.03 to 1.94)	19.59 (16.16 to 22.89)
European region	11,345.49 (8,039.09 to 15,305.62)	1.19 (0.84 to 1.62)	18,180.50 (12,982.34 to 24,289.37)	1.43 (1.02 to 1.94)	19.5 (16.05 to 22.79)
Latin America & Caribbean–World Bank	2,279.04 (1,544.00 to 3,249.16)	0.54 (0.37 to 0.75)	4,108.03 (2,828.90 to 5622.11)	0.61 (0.42 to 0.83)	11.93 (7.51 to 16.88)
Middle East & North Africa–World Bank	1,355.65 (911.51 to 1,936.11)	0.56 (0.37 to 0.78)	2,598.88 (1,734.69 to 3,673.83)	0.55 (0.37 to 0.77)	−1.60 (−3.51 to 0.41)
North America	5414.20 (3,851.51 to 7,341.12)	1.73 (1.23 to 2.32)	10,067.04 (7,304.85 to 13,260.40)	1.96 (1.42 to 2.59)	13.49 (4.92 to 22.96)
Northern Africa	578.80 (389.21 to 828.01)	0.49 (0.33 to 0.69)	1,018.95 (677.71 to 1,454.97)	0.49 (0.32 to 0.69)	−1.28 (−3.89 to 1.58)
Region of the Americas	7,667.74 (5,404.07 to 10,339.44)	1.15 (0.81 to 1.54)	14,141.02 (10,138.65 to 18,782.62)	1.19 (0.86 to 1.59)	3.77 (−2.40 to 9.91)
South Asia–World Bank	3,509.03 (2,223.12 to 5,122.79)	0.32 (0.21 to 0.45)	6,561.62 (4,271.42 to 9,468.68)	0.34 (0.22 to 0.48)	6.02 (3.43 to 9.09)
South-East Asia region	4,083.45 (2,610.86 to 5,965.07)	0.32 (0.21 to 0.45)	7,012.12 (4,566.23 to 10,071.02)	0.33 (0.22 to 0.48)	4.80 (2.47 to 7.41)
Southern Africa	296.32 (193.39 to 432.25)	0.34 (0.22 to 0.49)	555.51 (363.14 to 807.75)	0.32 (0.21 to 0.46)	−6.32 (−7.77 to −4.39)
Sub-Saharan Africa–World Bank	1,305.60 (847.11 to 1,902.25)	0.29 (0.19 to 0.41)	2,948.17 (1,889.30 to 4,301.74)	0.27 (0.18 to 0.39)	−5.06 (−6.11 to −3.68)
Western Africa	435.24 (280.48 to 636.60)	0.28 (0.18 to 0.40)	1,067.78 (678.34 to 1,561.98)	0.27 (0.18 to 0.38)	−4.00 (−5.36 to −2.42)
Western Pacific region	8,140.29 (5,443.43 to 11,425.74)	0.54 (0.37 to 0.75)	11,966.95 (8,269.12 to 16,320.98)	0.57 (0.39 to 0.79)	5.10 (1.33 to 9.52)
World Bank high income	16,729.25 (11,832.22 to 22,651.24)	1.43 (1.01 to 1.93)	30,076.19 (21,727.09 to 39,988.49)	1.67 (1.21 to 2.23)	17.44 (13.28 to 21.99)
World Bank low income	860.70 (570.57 to 1,242.45)	0.31 (0.21 to 0.44)	1,841.37 (1,198.64 to 2,661.58)	0.29 (0.20 to 0.41)	−6.81 (−8.15 to −5.31)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
World Bank lower middle income	6,702.25 (4,343.84 to 9,733.65)	0.35 (0.23 to 0.49)	11,879.66 (7,788.61 to 17,030.30)	0.34 (0.23 to 0.49)	–0.23 (–2.26 to 2.05)
World Bank upper middle income	10,100.56 (6,677.82 to 14,326.58)	0.50 (0.33 to 0.71)	14,044.91 (9,401.91 to 19,240.65)	0.54 (0.36 to 0.75)	6.30 (3.17 to 10.25)
YLLs					
Global	471,720.57 (427,708.75 to 507,715.98)	10.51 (9.70 to 11.20)	982,676.88 (904,588.13 to 1,064,643.84)	11.46 (10.52 to 12.43)	9.10 (–0.70 to 19.99)
Central Asia	198.82 (138.76 to 311.94)	0.27 (0.20 to 0.42)	986.37 (847.82 to 1,135.03)	1.03 (0.89 to 1.19)	280.01 (139.13 to 444.12)
Central Europe	12,438.59 (11,995.65 to 12,993.91)	10.33 (9.94 to 10.78)	31,072.15 (28,267.61 to 34,129.44)	18.97 (17.31 to 20.83)	83.57 (66.69 to 102.76)
Eastern Europe	8,398.63 (6,212.12 to 11,127.83)	3.43 (2.58 to 4.46)	62,662.5 (57,842.75 to 67,614.07)	20.3 (18.78 to 21.79)	492.4 (340.85 to 715.42)
Australasia	9,957.93 (9,544.89 to 10,345.23)	45.36 (43.57 to 47.05)	21,923.09 (19,692.14 to 24,213.83)	47.63 (43.19 to 52.29)	5.01 (–4.36 to 15.88)
High-income Asia Pacific	30,160.98 (28,702.64 to 31,091.76)	15.4 (14.57 to 15.95)	65,244.16 (58,315.31 to 70,652.65)	17.04 (15.63 to 18.25)	10.61 (3.95 to 18.88)
High-income North America	118,459.43 (114,613.38 to 121,073.19)	38.09 (37.03 to 38.86)	227,144.09 (214,476.30 to 236,497.91)	39.62 (37.84 to 41.12)	4.02 (0.02 to 7.72)
Southern Latin America	1,141.13 (1,102.15 to 1,177.85)	2.39 (2.31 to 2.47)	17,366.54 (15,771.00 to 19,036.85)	21.64 (19.63 to 23.68)	804.74 (720.15 to 895.00)
Western Europe	171,775.43 (167,040.70 to 175,100.87)	36.69 (35.72 to 37.34)	291,122.61 (264,527.26 to 319,733.25)	39.53 (36.24 to 43.25)	7.72 (–0.91 to 17.44)
Andean Latin America	32.78 (20.92 to 56.95)	0.13 (0.08 to 0.23)	4,701.81 (3,552.79 to 5,795.28)	7.61 (5.76 to 9.39)	5,732.04 (2,445.98 to 9,416.54)
Caribbean	121.19 (104.88 to 153.92)	0.39 (0.34 to 0.49)	6,359.41 (5,340.58 to 7,484.54)	12.18 (10.21 to 14.34)	3,020.61 (2,230.40 to 3,733.06)
Central Latin America	7,737.72 (7,508.24 to 8,006.09)	6.28 (6.13 to 6.45)	34,653.33 (30,275.49 to 39,337.37)	13.4 (11.68 to 15.20)	113.21 (84.95 to 142.91)
Tropical Latin America	12,370.19 (11,918.37 to 12,903.55)	10.33 (10.01 to 10.71)	55,366.53 (51,768.62 to 59,045.07)	21.62 (20.21 to 23.06)	109.35 (91.10 to 123.81)
North Africa and Middle East	11,294.35 (6,666.02 to 20,201.51)	3.01 (1.77 to 5.12)	25,464.21 (18,252.29 to 35,418.02)	4.71 (3.39 to 6.53)	56.59 (–13.53 to 182.49)
South Asia	1,389.53 (750.86 to 2,689.55)	0.16 (0.08 to 0.33)	12,089.10 (5,975.18 to 18,056.43)	0.74 (0.37 to 1.10)	374.08 (178.72 to 618.03)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
East Asia	84,720.33 (46,916.77 to 108,818.09)	7.51 (4.25 to 9.59)	121,285.39 (79,601.85 to 164,490.78)	7.24 (4.54 to 9.48)	−3.59 (−43.67 to 81.97)
Oceania	6.98 (4.41 to 10.12)	0.16 (0.09 to 0.22)	9.13 (6.73 to 13.20)	0.09 (0.07 to 0.12)	−42.97 (−59.39 to −5.78)
Southeast Asia	1,051.75 (534.97 to 1,564.15)	0.29 (0.15 to 0.44)	4,448.97 (2,898.08 to 6,429.13)	0.62 (0.41 to 0.90)	113.49 (36.78 to 221.23)
Central Sub-Saharan Africa	34.8 (21.49 to 51.44)	0.06 (0.04 to 0.09)	22.39 (13.54 to 52.45)	0.02 (0.01 to 0.06)	−63.30 (−78.06 to −21.04)
Eastern Sub-Saharan Africa	73.64 (53.71 to 96.65)	0.04 (0.02 to 0.05)	48.17 (28.25 to 99.47)	0.02 (0.01 to 0.03)	−56.7 (−69.74 to −17.27)
Southern Sub-Saharan Africa	231.11 (77.34 to 481.85)	0.51 (0.15 to 1.01)	266.09 (101.48 to 483.15)	0.32 (0.13 to 0.56)	−37.79 (−68.62 to 38.32)
Western Sub-Saharan Africa	125.26 (83.99 to 156.02)	0.06 (0.04 to 0.08)	440.86 (306.01 to 611.02)	0.10 (0.07 to 0.15)	70.36 (24.16 to 125.25)
Africa	796.75 (501.68 to 1,039.59)	0.12 (0.07 to 0.16)	1,214.51 (903.21 to 1,593.56)	0.12 (0.09 to 0.15)	−4.77 (−26.25 to 55.54)
African region	485.64 (289.83 to 724.94)	0.11 (0.06 to 0.16)	1,163.64 (864.76 to 1,502.95)	0.14 (0.11 to 0.18)	30.66 (−5.29 to 119.41)
America	139,824.47 (135,723.82 to 142,498.13)	21.93 (21.27 to 22.36)	344,356.31 (325,531.03 to 362,156.69)	27.06 (25.58 to 28.47)	23.36 (17.57 to 29.83)
Asia	129,224.24 (89,297.89 to 155,196.80)	4.73 (3.47 to 5.56)	230,698.52 (179,178.95 to 276,855.11)	4.65 (3.60 to 5.58)	−1.65 (−25.59 to 36.96)
Central Africa	42.69 (29.74 to 58.03)	0.06 (0.04 to 0.09)	61.14 (40.35 to 96.06)	0.04 (0.03 to 0.07)	−29.06 (−54.89 to 17.89)
Commonwealth high income	54,852.31 (53,506.84 to 55,745.95)	41.35 (40.45 to 41.99)	102,325.08 (94,974.75 to 109,233.13)	44.37 (41.66 to 47.21)	7.30 (1.57 to 14.27)
Commonwealth low income	123.10 (78.68 to 190.26)	0.06 (0.03 to 0.12)	759.19 (271.38 to 1,399.81)	0.26 (0.08 to 0.49)	327.55 (151.81 to 585.21)
Commonwealth middle income	1,734.27 (964.66 to 2,912.05)	0.18 (0.09 to 0.33)	13,733.35 (7,657.55 to 19,307.06)	0.76 (0.42 to 1.07)	323.17 (168.42 to 505.10)
East Asia & Pacific–World Bank	125,908.25 (86,743.84 to 150,753.31)	7.67 (5.52 to 9.06)	211,988.88 (165,428.47 to 256,662.30)	7.23 (5.52 to 8.83)	−5.84 (−31.47 to 37.21)
Eastern Africa	75.40 (60.46 to 94.16)	0.05 (0.04 to 0.06)	411.59 (368.19 to 462.32)	0.21 (0.19 to 0.23)	330.26 (243.64 to 449.1)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
Eastern Mediterranean region	1,103.77 (796.27 to 1,533.41)	0.28 (0.20 to 0.41)	4,418.16 (3,301.23 to 5,574.83)	0.72 (0.54 to 0.91)	153.58 (90.36 to 234.14)
Europe	201,490.02 (193,687.20 to 213,145.62)	22.52 (21.59 to 24.17)	404,439.38 (373,856.47 to 438,649.23)	31.58 (29.28 to 34.29)	40.23 (28.43 to 55.68)
Europe & Central Asia–World Bank	201,234.68 (193,428.36 to 212,844.43)	21.32 (20.44 to 22.81)	404,357.07 (373,844.74 to 438,516.43)	29.64 (27.49 to 32.15)	39.00 (27.25 to 54.09)
European region	202,703.56 (194,875.59 to 214,347.95)	21.32 (20.45 to 22.82)	407,475.52 (376,659.79 to 441,837.91)	29.53 (27.39 to 32.03)	38.46 (26.81 to 53.43)
Latin America & Caribbean–World Bank	21,398.24 (20,881.11 to 22,086.22)	6.07 (5.93 to 6.23)	118,217.14 (108,552.05 to 128,327.41)	16.72 (15.33 to 18.17)	175.50 (151.74 to 201.31)
Middle East & North Africa–World Bank	2,284.82 (2,018.07 to 2,647.48)	1.22 (1.11 to 1.36)	5,917.35 (5,238.3 to 6,613.56)	1.57 (1.40 to 1.74)	28.61 (12.74 to 47.04)
North America	118,453.27 (114,607.02 to 121,067.97)	38.09 (37.02 to 38.86)	227,148.47 (214,480.11 to 236,501.64)	39.62 (37.84 to 41.12)	4.03 (0.03 to 7.73)
Northern Africa	314.41 (202.73 to 456.71)	0.21 (0.13 to 0.30)	67.67 (40.81 to 212.69)	0.04 (0.02 to 0.11)	−83.58 (−90.28 to −34.84)
Region of the Americas	139,824.47 (135,723.82 to 142,498.13)	21.93 (21.27 to 22.36)	344,356.31 (325,531.03 to 362,156.69)	27.06 (25.58 to 28.47)	23.36 (17.57 to 29.83)
South Asia–World Bank	1,446.43 (799.33 to 2,763.78)	0.16 (0.08 to 0.33)	12,752.91 (6,327.09 to 18,821.93)	0.76 (0.38 to 1.12)	378.42 (180.14 to 624.4)
South-East Asia region	2,562.13 (1,380.45 to 4,261.10)	0.24 (0.12 to 0.41)	14,150.87 (7,106.03 to 21,228.78)	0.73 (0.37 to 1.09)	208.04 (96.16 to 350.19)
Southern Africa	252.02 (95.96 to 504)	0.33 (0.10 to 0.62)	281.31 (111.88 to 506.68)	0.17 (0.07 to 0.30)	−47.25 (−74.19 to 19.84)
Sub-Saharan Africa–World Bank	483.75 (289.24 to 724.72)	0.11 (0.06 to 0.16)	1,150.46 (852.74 to 1,477.50)	0.14 (0.11 to 0.18)	30.48 (−5.13 to 118.51)
Western Africa	112.23 (75.65 to 139.50)	0.06 (0.04 to 0.07)	392.80 (270.53 to 551.31)	0.10 (0.07 to 0.15)	72.76 (26.04 to 133.81)
Western Pacific region	122,778.11 (84,182.66 to 147,256.01)	8.97 (6.39 to 10.64)	204,201.15 (158,588.36 to 248,046.34)	8.43 (6.36 to 10.34)	−6.04 (−33.03 to 38.99)
World Bank high income	345,243.1 (335,526.57 to 350,941.38)	30.48 (29.73 to 30.96)	653,693.09 (604,984.75 to 701,012.81)	33.59 (31.48 to 35.83)	10.20 (3.88 to 16.93)
World Bank low income	845.95 (439.21 to 1,435.91)	0.29 (0.15 to 0.50)	902.75 (454.87 to 1,910.01)	0.19 (0.10 to 0.39)	−34.56 (−62.26 to 17.08)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
World Bank lower middle income	5,955.37 (4,194.38 to 8,540.97)	0.38 (0.25 to 0.56)	24,038.84 (15,910.25 to 31,412.37)	0.82 (0.55 to 1.07)	117.35 (51.36 to 207.88)
World Bank upper middle income	119,320.93 (78,206.85 to 150,418.33)	6.17 (4.13 to 7.74)	303,083.42 (250,975.94 to 353,547.85)	9.63 (7.87 to 11.26)	56.21 (12.57 to 131.10)
Death					
Global	15,260.07 (14,366.61 to 16,042.60)	0.38 (0.36 to 0.40)	39,081.64 (35,756.51 to 42,432.82)	0.46 (0.42 to 0.49)	19.84 (10.79 to 30.39)
Central Asia	3.44 (2.53 to 5.21)	0.01 (0.00 to 0.01)	25.93 (22.52 to 29.98)	0.03 (0.02 to 0.03)	429.46 (231.44 to 627.85)
Central Europe	310.22 (298.56 to 325.03)	0.23 (0.22 to 0.24)	1,125.06 (1,025.82 to 1,237.80)	0.57 (0.52 to 0.63)	150.58 (126.24 to 177.58)
Eastern Europe	226.39 (163.44 to 311.51)	0.09 (0.06 to 0.12)	2,174.77 (1,996.69 to 2,365.57)	0.64 (0.59 to 0.70)	652.78 (447.20 to 977.34)
Australasia	374.92 (354.19 to 391.42)	1.60 (1.52 to 1.67)	959.91 (845.61 to 1,068.1)	1.84 (1.64 to 2.03)	14.53 (3.92 to 27.00)
High-income Asia Pacific	1,095.25 (1,046.06 to 1,130.28)	0.54 (0.52 to 0.56)	3,289.81 (2,881.94 to 3,613.6)	0.72 (0.64 to 0.78)	32.17 (22.46 to 42.29)
High-income North America	4,327.85 (4,109.63 to 4,454.87)	1.27 (1.21 to 1.30)	9,570.87 (8,808.62 to 10,050.59)	1.50 (1.39 to 1.57)	18.23 (13.56 to 22.72)
Southern Latin America	35.07 (33.86 to 36.36)	0.07 (0.07 to 0.08)	636.82 (578.51 to 704.09)	0.75 (0.68 to 0.83)	909.01 (813.56 to 1,010.73)
Western Europe	6,548.69 (6,289.31 to 6,711.32)	1.20 (1.16 to 1.23)	13,100.07 (11,684.80 to 14,514.26)	1.49 (1.35 to 1.64)	24.33 (14.49 to 36.22)
Andean Latin America	0.94 (0.59 to 1.64)	0.00 (0.00 to 0.01)	159.69 (122.85 to 195.55)	0.27 (0.21 to 0.32)	6,195.47 (2,688.82 to 10,110.73)
Caribbean	3.19 (2.84 to 3.84)	0.01 (0.01 to 0.01)	222.99 (187.92 to 261.73)	0.42 (0.35 to 0.49)	3,572.45 (2,658.33 to 4,424.48)
Central Latin America	185.73 (181.44 to 190.44)	0.19 (0.18 to 0.19)	1,109.34 (972.92 to 1,261.12)	0.43 (0.38 to 0.49)	133.76 (103.84 to 166.03)
Tropical Latin America	313.75 (303.59 to 324.77)	0.30 (0.29 to 0.31)	1,876.55 (1,748.35 to 2,009.62)	0.73 (0.68 to 0.78)	140.21 (122.64 to 155.64)
North Africa and Middle East	179.48 (105.70 to 301.97)	0.06 (0.03 to 0.10)	698.85 (482.33 to 980.86)	0.14 (0.10 to 0.20)	125.83 (28.11 to 319.20)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
South Asia	32.10 (15.96 to 69.31)	0.00 (0.00 to 0.01)	347.67 (168.30 to 522.09)	0.02 (0.01 to 0.03)	392.98 (176.45 to 705.33)
East Asia	1588.58 (900.19 to 2016.74)	0.15 (0.09 to 0.19)	3,630.95 (2,395.89 to 4,966.82)	0.18 (0.12 to 0.25)	20.85 (–24.51 to 116.11)
Oceania	0.17 (0.11 to 0.24)	0.01 (0.00 to 0.01)	0.24 (0.18 to 0.32)	0.00 (0.00 to 0.00)	–44.99 (–60.93 to 0.14)
Southeast Asia	25.63 (12.77 to 39.22)	0.01 (0.00 to 0.01)	137.32 (91.46 to 195.19)	0.02 (0.01 to 0.03)	136.57 (47.96 to 259.8)
Central Sub-Saharan Africa	0.62 (0.42 to 0.86)	0.00 (0.00 to 0.00)	0.49 (0.29 to 1.21)	0.00 (0.00 to 0.00)	–62.08 (–76.85 to –12.00)
Eastern Sub-Saharan Africa	1.22 (0.83 to 1.64)	0.00 (0.00 to 0.00)	1.01 (0.61 to 2.21)	0.00 (0.00 to 0.00)	–54.02 (–67.63 to –12.91)
Southern Sub-Saharan Africa	4.88 (1.4 to 8.9)	0.01 (0.00 to 0.02)	5.44 (2.20 to 9.46)	0.01 (0 to 0.01)	–43.54 (–66.63 to 38)
Western Sub-Saharan Africa	1.97 (1.28 to 2.48)	0.00 (0.00 to 0.00)	7.89 (5.53 to 11.18)	0.00 (0.00 to 0.00)	81.48 (28.45 to 146.97)
Africa	13.70 (7.90 to 17.42)	0.00 (0.00 to 0.00)	28.59 (22.79 to 36.45)	0.00 (0.00 to 0.00)	17.93 (–4.49 to 110.35)
African region	9.22 (4.87 to 12.94)	0.00 (0.00 to 0.00)	27.36 (21.62 to 33.83)	0.00 (0.00 to 0.01)	51.87 (21.39 to 188.03)
America	4,865.38 (4,635.17 to 4,998.02)	0.78 (0.74 to 0.80)	13,529.81 (12,547.10 to 14,297.48)	1.02 (0.94 to 1.07)	29.83 (24.00 to 36.21)
Asia	3,167.78 (2,409.81 to 3,665.06)	0.14 (0.11 to 0.16)	8,553.49 (7,010.38 to 10,160.32)	0.17 (0.14 to 0.20)	23.37 (0.12 to 51.51)
Central Africa	0.74 (0.49 to 1.00)	0.00 (0.00 to 0.00)	1.16 (0.77 to 1.89)	0.00 (0.00 to 0.00)	–34.50 (–60.18 to 18.54)
Commonwealth high income	2,148.24 (2,071.31 to 2,191.32)	1.45 (1.41 to 1.48)	4,605.26 (4,181.22 to 4,959.37)	1.74 (1.59 to 1.87)	19.63 (12.67 to 27.86)
Commonwealth low income	2.20 (1.19 to 4.06)	0.00 (0.00 to 0.00)	21.45 (6.62 to 41.22)	0.01 (0.00 to 0.02)	434.69 (200.06 to 833.67)
Commonwealth middle income	39.60 (20.03 to 73.95)	0.01 (0.00 to 0.01)	397.02 (222.49 to 562.04)	0.02 (0.01 to 0.03)	364.36 (178.98 to 583.5)
East Asia & Pacific–World Bank	3,083.85 (2,346.02 to 3,541.39)	0.21 (0.17 to 0.24)	7,986.51 (6,604.33 to 9,536.38)	0.25 (0.21 to 0.30)	18.25 (–5.70 to 49.70)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
Eastern Africa	1.45 (1.14 to 1.79)	0.00 (0.00 to 0.00)	12.93 (11.61 to 14.23)	0.01 (0.01 to 0.01)	456.91 (309.71 to 660.39)
Eastern Mediterranean region	19.12 (13.45 to 27.51)	0.01 (0.00 to 0.01)	113.80 (85.85 to 143.36)	0.02 (0.02 to 0.03)	228.02 (129.45 to 350.99)
Europe	7,201.6 (6,880.05 to 7,482.99)	0.72 (0.69 to 0.75)	16,894.76 (15,348.35 to 18,501.86)	1.12 (1.03 to 1.23)	55.53 (43.77 to 71.11)
Europe & Central Asia–World Bank	7,194.69 (6,873.45 to 7,474.86)	0.70 (0.67 to 0.73)	16,885.49 (15,341.11 to 18,490.21)	1.08 (0.99 to 1.17)	54.53 (42.84 to 69.98)
European region	7,239.98 (6,917.66 to 7,522.16)	0.70 (0.66 to 0.73)	17,011.99 (15,457.14 to 18,628.19)	1.07 (0.98 to 1.17)	54.14 (42.48 to 69.49)
Latin America & Caribbean–World Bank	538.55 (525.39 to 551.69)	0.18 (0.17 to 0.18)	3,997.26 (3,681.58 to 4,352.57)	0.56 (0.52 to 0.61)	218.38 (193.8 to 245.48)
Middle East & North Africa–World Bank	58.81 (53.73 to 65.58)	0.04 (0.04 to 0.05)	201.93 (181.30 to 223.45)	0.06 (0.06 to 0.07)	39.37 (22.65 to 56.44)
North America	4,327.66 (4,109.44 to 4,454.67)	1.27 (1.21 to 1.30)	9,571.03 (8,808.74 to 10,050.68)	1.50 (1.39 to 1.57)	18.23 (13.56 to 22.73)
Northern Africa	4.54 (2.84 to 6.35)	0.00 (0.00 to 0.01)	1.71 (1.05 to 5.27)	0.00 (0.00 to 0.00)	−73.93 (−83.59 to 1.85)
Region of the Americas	4,865.38 (4,635.17 to 4,998.02)	0.78 (0.74 to 0.80)	13,529.81 (12,547.1 to 14,297.48)	1.02 (0.94 to 1.07)	29.83 (24.00 to 36.21)
South Asia–World Bank	33.60 (17.05 to 71.38)	0.00 (0.00 to 0.01)	369.71 (181.49 to 548.83)	0.02 (0.01 to 0.03)	401.61 (182.09 to 717.63)
South-East Asia region	57.85 (29.93 to 102.84)	0.01 (0.00 to 0.01)	420.27 (212.16 to 625.33)	0.02 (0.01 to 0.03)	238.44 (108.21 to 405.01)
Southern Africa	5.21 (1.67 to 9.22)	0.01 (0.00 to 0.01)	5.74 (2.40 to 9.81)	0.00 (0.00 to 0.01)	−49.23 (−69.52 to 25.01)
Sub-Saharan Africa–World Bank	9.19 (4.86 to 12.93)	0.00 (0.00 to 0.00)	26.94 (21.36 to 33.44)	0.00 (0.00 to 0.00)	51.91 (21.66 to 188.66)
Western Africa	1.76 (1.16 to 2.22)	0.00 (0.00 to 0.00)	7.04 (4.93 to 10.15)	0.00 (0.00 to 0.00)	84.81 (29.84 to 153.71)
Western Pacific region	3,011.43 (2,286.92 to 3,462.09)	0.24 (0.19 to 0.28)	7,743.64 (6,382.32 to 9,234.41)	0.29 (0.23 to 0.34)	17.19 (−7.17 to 49.83)
World Bank high income	12,722.96 (12,158.83 to 13,006.43)	1.02 (0.97 to 1.04)	28,638.89 (25,732.41 to 31,046.28)	1.27 (1.16 to 1.37)	24.84 (17.52 to 33.25)

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Table 2. Continued

Variable	1990		2021		Percentage change in age-standardized rates between 1990 and 2021 (%)
	Counts (95% UI)	Age-standardized rate (per 100,000 people)	Counts (95% UI)	Age-standardized rate (per 100,000 people)	
World Bank low income	16.65 (8.65 to 28.57)	0.01 (0.00 to 0.01)	23.32 (12.21 to 48.34)	0.01 (0.00 to 0.01)	–22.67 (–54.46 to 45.72)
World Bank lower middle income	134.35 (88.15 to 201.03)	0.01 (0.01 to 0.02)	690.19 (460.95 to 897.12)	0.03 (0.02 to 0.03)	151.88 (68.84 to 269.35)
World Bank upper middle income	2,375.41 (1,612.35 to 2,953.04)	0.13 (0.09 to 0.17)	9,692.75 (8,218.16 to 11,210.52)	0.28 (0.24 to 0.33)	110.57 (58.78 to 189.46)

DALYs, disability-adjusted life years; GBD, Global Burden of Disease; UI, uncertainty interval; YLDs, years lived with disability; YLLs, years of life lost.

Discussion

Key results

This study described changes in global MND burden from 1990 to 2021. The numbers of prevalent and incident cases increased substantially, but their age-standardized rates declined slightly. Conversely, age-standardized mortality, YLL, and DALY rates increased. This divergence suggests that population growth and aging contributed substantially to the rise in absolute case numbers, rather than a generalized increase in age-standardized disease occurrence. The increasing burden of mortality and premature death nevertheless underscores the need for healthcare planning at global, regional, and national levels.

Interpretation

Our findings indicate that MND burden may differ across geographic regions. Variation in diagnostic and reporting capacity may contribute to these differences; genetic and environmental explanations remain hypotheses requiring further investigation. Previous studies reported higher ALS incidence among populations of European ancestry than among Asian populations [8,20,21]. A meta-analysis of 45 geographic regions found consistent ALS incidence among populations of European descent in New Zealand, Europe, and North America, at 1.81 (1.66–1.97) per 100,000 person-years. This exceeded rates in South and East Asian populations, at 0.83 (0.42–1.24) and 0.73 (0.58–0.89) per 100,000 person-years, respectively [8]. C9ORF72, the leading genetic contributor to ALS and responsible for 40% of familial and 8% of sporadic cases, may help explain the higher incidence in Europe and North America [22]. However, the sharp decline in ALS incidence after westernization in Guam and Japan's Kii Peninsula suggests that both environmental and genetic factors likely influence incidence [23].

Across continents, SDI-related patterns in DALYs and MND mortality closely resembled those in prevalence. High-SDI regions and countries generally had higher age-standardized DALYs, except in high-income Asia Pacific, whereas middle- and low-SDI regions had relatively lower counts and rates. Riluzole therapy, noninvasive ventilation, and multidisciplinary care may prolong survival, thereby increasing prevalence and YLDs among diagnosed patients [24-27], but survival gains alone cannot explain the simultaneous rise in mortality rates. More complete case ascertainment, greater access to neurological assessment, established disease registries, and more accurate cause-of-death certification may contribute to the higher recorded burden in high-SDI settings. Conversely, underdiagnosis and incomplete mortality registration may lead to underestimation in lower-SDI settings.

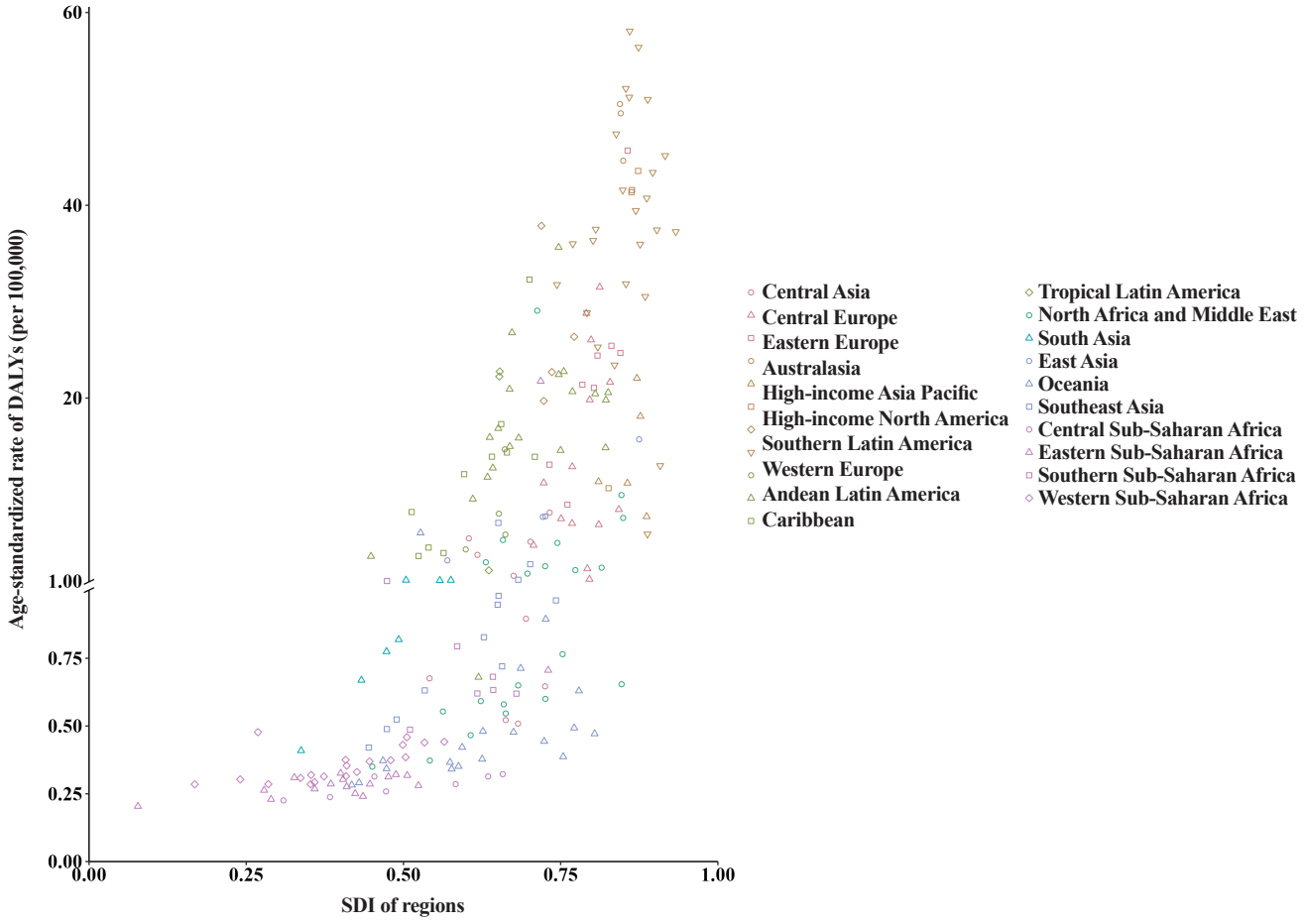


Fig. 3. Age-standardized disability-adjusted life year (DALY) rates per 100,000 people by regional Socio-demographic Index (SDI).

Because GBD lacks individual-level diagnostic, treatment, and survival data, these mechanisms are possible explanations rather than causal findings.

In this study, the age-standardized DALY rate increased significantly after age 50, peaked at ages 70–79, and then declined rapidly in both men and women, consistent with the known age distribution of ALS [28,29]. Non-ALS MNDs, such as spinal muscular atrophy and hereditary spastic paraplegia, likely account for the small peak in early childhood. These age patterns should be interpreted as composite findings because GBD does not distinguish MND subtypes.

The study's broad geographic scope is a major strength, permitting standardized comparisons across 204 countries and territories and 21 GBD regions. Whereas a recent MND-specific analysis of GBD 2023 examined China [30], this study compares countries and regions worldwide.

Limitations

This study has several limitations inherent in GBD [31]. First, MND case ascertainment is difficult, and under-recognition is plausible, especially among older adults and ethnic minority populations. Second, differences between subtypes could not be examined because IHME releases only pooled estimates for all MND phenotypes. Third, inputs came from ICD-coded administrative claims and systematic reviews rather than a cluster-random sample, precluding statistically robust state-level comparisons. Fourth, GBD does not explicitly model time-varying factors that may affect coding and reporting, including the transition from ICD-9 to ICD-10, regulatory approvals of riluzole and edaravone, and healthcare-service conditions; these factors may have introduced secular ascertainment bias. Administrative datasets are also susceptible to miscoding. Previous studies support the use of ICD codes to identify MNDs, reporting positive predictive values of 92% (95% confidence interval [CI], 89–95) for ICD-9 codes in US hospital admissions and 65% (95% CI, 59–70), with 85% sensitivity (95% CI, 80–89), for ICD-10 codes in US death certificates [32,33]. However, cases could not be validated because individual medical records were unavailable. Fifth, although GBD

2021 specifies the El Escorial criteria as the primary ALS diagnostic standard, ICD codes may reflect clinical suspicion without full concordance with these criteria, allowing a mismatch between codes and criteria. Sixth, GBD 2021 modeled severity exclusively using ALS because severity data for other MND subtypes were unavailable; disability estimates may therefore not generalize to the full MND spectrum. Finally, this analysis used GBD 2021 estimates. Because GBD 2023 data have since become available, estimates based on updated sources and modeling procedures may differ.

Suggestions

Our findings suggest that population-based MND registries should be strengthened, especially in low- and middle-SDI regions where underdiagnosis and limited reporting may lead to underestimation of the true burden. Health systems should also prepare for greater demand for multidisciplinary care as populations age.

Conclusion

GBD 2021 provides comprehensive, methodologically consistent estimates of MND epidemiology and societal burden worldwide. The substantial increase in absolute case numbers from 1990 to 2021 occurred alongside slight declines in age-standardized prevalence and incidence rates. Age-standardized mortality, YLL, and DALY rates, by contrast, increased. These divergent trends indicate increasing absolute healthcare needs associated with demographic change alongside a rising mortality-related burden.

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Conceptualization: JIS, TJS. Data curation: JHP, DKY, MSK, YC, SP. Formal analysis: JHP, DKY, MSK, YC, SP. Methodology: JHP, DKY, MSK, YC, SP. Validation: JHP, DKY, MSK, YC, SP. Project administration: JIS, TJS. Funding acquisition: JIS, TJS. Writing–original draft: JHP, DKY, MSK, YC, SP. Writing–review & editing: JHP, DKY, MSK, YC, SP, GBD 2021 Motor Neuron Diseases Collaborators, JIS, TJS. Final approval of the manuscript: all authors.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

The data used in these analyses can be downloaded from the GHDx website at https://ghdx.healthdata.org.

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None.

Supplementary materials

Supplementary files are available from https://doi.org/10.7910/DVN/2FIYUA

Supplement 1. Supplementary methods.

Supplement 2. Supplementary tables.

Table S1. Counts, age-standardized rates, and percentage changes in prevalence, incidence, disability-adjusted life years, years lived with disability, years of life lost and mortality for motor neuron diseases over time, both sexes, by Global Burden of Disease regions, 1990–2021.

Table S2. Counts, age-standardized rates, and percentage changes in prevalence, incidence, disability-adjusted life years, years lived with disability, years of life lost and mortality for motor neuron diseases over time, both sexes, by countries and territories, 1990–2021.

Supplement 3. Supplementary figures.

Fig. S1. Age-standardized (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death rate and count by year for motor neuron disease, 1990–2021, global.

Fig. S2. Age-standardized (A) prevalence, (B) incidence, (C) YLDs, (D) YLLs, (E) death rate and count by year and sex for motor neuron disease, 1990–2021, global.

Fig. S3. (A) Prevalence, (B) incidence, (C) YLDs, (D) YLLs, (E) death rate and count by age-groups for motor neuron disease, 2021, global.

Fig. S4. Count of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death by year for motor neuron disease, 1990–2021, global.

Fig. S5. Age-standardized and all age (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death rate by year for motor neuron disease, 1990–2021, global.

Fig. S6_1. Age-standardized rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease by sex, global, GBD regions, and GBD custom region.

Fig. S6_2. Age-standardized rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease by sex, global, SDI quintiles, GBD regions, and GBD custom region.

Fig. S7. Age-standardized (A) prevalence, (B) incidence, (C) YLDs, (D) YLLs, (E) death rate for motor neuron disease, 2021, global.

Fig. S8. Percentage change in age-standardized rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease, 1990–2021, global.

Fig. S9_1. Change in age-standardized rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease, 2000–2010 and 2010–2021, global, GBD regions, and GBD custom region.

Fig. S9_2. Change in age-standardized rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease, 2000–2010 and 2010–2021, global, SDI quintiles, GBD regions, and GBD custom region.

Fig. S10_1. Percentage change in age-standardized rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease, 1990–2021, global, GBD regions, and GBD custom region.

Fig. S10_2. Percentage change in age-standardized rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease, 1990–2021, global, SDI quintiles, GBD regions, and GBD custom region.

Fig. S11_1. Percentage change in all age counts of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease, 1990–2021, global, GBD regions, and GBD custom region.

Fig. S11_2. Percentage change in all age counts of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease, 1990–2021, global, SDI quintiles, GBD regions, and GBD custom region.

Fig. S12. Percentage change in age-standardized rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease, 2021, global, Africa, Asia, and Europe.

Fig. S13. Age-standardized rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease by years, 1990–2021, GBD region.

Fig. S14. Age-standardized rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease by years, 1990–2021, GBD region.

Fig. S15. Percentage change in age-standardized rate and number of (A)prevalence, (B)incidence, (C)DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease by age and sex, 1990–2021, global.

Fig. S16. Percent contribution of YLL and YLD in all-age DALYs of motor neuron disease, 1990–2021, global.

Fig. S17. Age-standardized rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs,YLLs, (F) death rate by year for motor neuron disease by SDI quintile, 1990–2021, global.

Fig. S18. Total (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death rate by age for motor neuron disease, 2021, SDI quintiles.

Fig. S19. Percentage change in total (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death rate by age for motor neuron disease, 1990–2021, SDI quintiles.

Fig. S20. Total rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease by age groups, 2021, SDI quintiles.

Fig. S21. Total rates of (A) prevalence, (B) incidence, (C) DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease for both sexes at the World Bank income level, by age group, 2021.

Fig. S22. Age-standardized rate and number of (A) incidence, (B) DALYs, (C) death for motor neuron disease by sex and years, 1990–2021, SDI quintiles.

Fig. S23. Relationships between the Socio-demographic Index

(SDI) and age-standardized rates of (A) DALYs, (B) mortality, and (C) incidence for motor neuron diseases, both sexes.

Fig. S24. Percentage change in age-standardized rate and number of (A)prevalence, (B)incidence, (C)DALYs, (D) YLDs, (E) YLLs, (F) death for motor neuron disease by age and sex, 1990–2021, SDI quintiles.

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Psoas–lumbar vertebral index and short-term pain relief after pulsed radiofrequency treatment of the dorsal root ganglion in postherpetic neuralgia in Korea: a retrospective pilot study

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Purpose: The psoas–lumbar vertebral index (PLVI), a marker of central sarcopenia measured using computed tomography (CT) or magnetic resonance imaging (MRI), has been linked to the development of postherpetic neuralgia (PHN). Whether PLVI predicts short-term pain relief after pulsed radiofrequency (pRF) treatment of the dorsal root ganglion (DRG) in established PHN remains unknown. This pilot study examined the association between PLVI and the reduction in numeric rating scale (NRS) pain scores 1 month after pRF.

Methods: Patients with PHN who underwent DRG pRF and had CT or MRI scans available for PLVI measurement were retrospectively reviewed. Correlations of the NRS reduction rate with PLVI and other variables were assessed, with 95% confidence intervals (CIs). Patients were divided into low- and high-PLVI groups using sex-specific medians and compared; multivariable regression was adjusted for sex. A supplementary responder analysis used thresholds of ≥30% and ≥50% reduction.

Results: In 19 patients, NRS scores decreased from 4.8±1.7 to 3.2±1.7, with a reduction rate of 29.3%±34.0%. PLVI was not significantly correlated with the reduction rate (r=−0.17; 95% CI, −0.58 to 0.31; P=0.49); neither the reduction rate (P=0.71) nor responder rates differed between the low- and high-PLVI groups. Male sex was associated with a smaller reduction (adjusted B=−47.2 percentage points; 95% CI, −90.9 to −3.5; P=0.036), although the unadjusted group comparison was not significant (Welch P=0.051) and 15 variables were tested without correction for multiple comparisons.

Conclusion: This pilot cohort showed no detectable association between PLVI and short-term pain relief after pRF; its small size precludes establishing the absence of an association. The exploratory sex difference warrants investigation in larger prospective studies with comprehensive sarcopenia assessment.

Keywords: Neuralgia, postherpetic; Herpes zoster; Pulsed radiofrequency treatment; Sarcopenia; Psoas muscles; Republic of Korea

Introduction

Background/rationale

Postherpetic neuralgia (PHN), the most common complication of herpes zoster (HZ), disproportionately affects older adults and reportedly occurs in 8%–24% of HZ cases [1]. Its pathogenesis is thought to involve peripheral and central sensitization after viral damage to the dorsal root ganglion (DRG) [2]. Pulsed radiofrequency (pRF) treatment of the DRG is an established intervention for PHN refractory to pharmacological therapy; when combined with standard medical treatment, it improves pain scores and reduces analgesic requirements [2]. Sarcopenia is an age-related loss of skeletal muscle mass and a core component of the frailty phenotype. It can be quantified using the psoas–lumbar vertebral index (PLVI), calculated as the mean cross-sectional area (CSA) of the bilateral psoas muscles divided by the L4 vertebral body area. This simple, reproducible marker requires no dedicated body-composition software [1,3]. Low PLVI has been linked to adverse outcomes in surgical and interventional settings, including degenerative spine surgery [3], morbidity and mortality in older patients with trauma or hip fracture [4], and postoperative acute kidney injury after hip fracture surgery [5].

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An et al. [1] reported that low PLVI independently predicted PHN development in patients aged ≥60 years with HZ, prompting the question of whether PLVI also predicts treatment response after PHN is established. Evidence from related interventional pain settings is mixed. Sarcopenia defined by the psoas muscle index was associated with slower pain improvement after radiofrequency ablation for lumbar facetogenic pain, but PLVI itself did not predict response in that cohort [6]. High-grade fatty infiltration of the cervical multifidus independently predicted a poor response to cervical epidural steroid injection [7], whereas PLVI correlated with a validated frailty scale but not with postoperative complications in a surgical spine cohort [3]. In addition to central sarcopenia, PHN risk and severity have been linked to delayed initiation of supplemental analgesia after HZ onset [8]. Once PHN is established, they have also been linked to central sensitization (brush-evoked allodynia), anxiety, depression, and younger age rather than the extent of peripheral nerve fiber damage [9].

Interventional treatments for established PHN vary in efficacy across targets and protocols. Studies of angulus costae pRF [10], computed tomography (CT)-guided thoracic nerve root coblation [11], DRG pRF combined with gabapentin [2], pRF with device-based pain assessment [12], and ultrasound-guided intercostal nerve pRF [13] all reported benefits over pharmacotherapy alone. However, response definitions and follow-up durations differed considerably, and none examined whether sarcopenia or frailty modifies treatment response. Recent evidence-based Korean Pain Society guidelines recommend pRF combined with medication for refractory PHN (recommendation grade: general use, strong; level of evidence: low), reserving spinal cord stimulation (SCS) as an elective next step after an inadequate response to pRF or nerve blocks [14]. Consistent with this hierarchy, a randomized trial in older patients with PHN found a substantially higher 12-month effective rate with short-term SCS than with pRF (79.3% vs. 42.1%) [15], although an earlier trial in a similar population found no significant difference between the techniques [16]. Because our cohort also consisted of older patients, these findings raise the possibility that age-related factors, potentially including central sarcopenia, influence the durability of the pRF response.

Objectives

Given the heterogeneity of procedures and sarcopenia markers, and the lack of prior studies specifically examining PLVI in relation to pRF outcomes in PHN, we conducted a retrospective pilot analysis. We tested the hypothesis that lower PLVI is associated with a smaller reduction in numeric rating scale (NRS) pain scores from baseline to 1 month after DRG pRF in patients with PHN.

Methods

Ethics statement

The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital (approval no. 2026-05-038-002). The board waived informed consent because the study was retrospective.

Study design

This was a single-center retrospective analysis.

Setting

Patients were considered for inclusion if they attended the outpatient pain clinic of Ewha Womans University Mokdong Hospital between 2016 and 2026, received a PHN diagnosis based on clinical history and neurological examination, and subsequently underwent DRG pRF.

Participants

PHN was defined as dermatomal neuropathic pain that persisted after resolution of the HZ rash, consistent with contemporary clinical definitions requiring pain beyond approximately 1 month after rash onset [14]. Before pRF, all patients had pain refractory to first-line pharmacological therapy with gabapentinoids, tricyclic antidepressants, and/or lidocaine patches.

Patients without cross-sectional imaging for measurement of the lumbar psoas muscles and L4 vertebral body were excluded. For patients who underwent multiple pRF procedures during the study period, only the first treatment episode was included, yielding a final analytic sample of 19 patients.

Pulsed radiofrequency procedure

An experienced pain physician (W.J.K.) performed DRG pRF under fluoroscopic guidance at the spinal segment(s) corresponding to each patient's dermatomal pain distribution, using a technique consistent with previously described PHN protocols [2]. After satisfactory local anesthesia, a radiofrequency cannula (22G, 10-mm active tip) was advanced under fluoroscopic guidance toward the intervertebral foramen at the affected DRG level. Appropriate sensory stimulation thresholds were confirmed before treatment to ensure accurate needle placement. Radiofrequency current was then delivered in 3 treatment cycles at standard settings: output voltage, 45 V; pulse frequency, 2 Hz; pulse width, 20 ms; upper temperature limit, 42°C; and duration, 120 seconds per cycle. This uniformly applied routine technique was broadly consistent with previous studies of DRG pRF for PHN [2]. Treat-

ment was delivered at a thoracic level in 16 of the 19 patients (84.2%), at a sacral level in 2 (10.5%; both S1), and at a lumbar level in 1 (5.3%; L3); T3 and T4 were the most frequently treated individual levels (4 patients each). Concomitant pharmacological therapy with gabapentinoids and/or other adjunctive analgesics continued at the treating physician's discretion and was not standardized for this retrospective analysis.

Variables

The primary outcome was the NRS reduction rate, defined as the percentage decrease in the NRS pain score (0–10) from baseline to the 1-month follow-up after pRF: (NRS at baseline−NRS at 1 month)/NRS at baseline × 100. Baseline NRS scores were recorded immediately before pRF, and 1-month scores at each patient's first postprocedural follow-up visit. Absolute NRS reduction (baseline NRS−1-month NRS, in points) was also calculated as a secondary descriptive measure of pain relief. The NRS reduction rate was the dependent variable in all correlation, group-comparison, and regression analyses described below. Responders were additionally defined as patients with a ≥30% or ≥50% decrease in NRS score from baseline to 1 month.

Data sources and measurement

Central sarcopenia was quantified using PLVI, calculated as the mean CSA of the bilateral psoas muscles divided by the CSA of the L4 vertebral body at the inferior endplate level on axial CT or magnetic resonance imaging (MRI): PLVI = [(right psoas CSA+left psoas CSA)/2]/L4 vertebral body CSA. This followed previously published methodology [1,3,4]. PLVI cutoff strategies for sarcopenia vary across studies: some use the lowest sex-specific quartile (e.g., PLVI < 0.57 in men and < 0.43 in women in a hip fracture cohort) [5], whereas others, including this study, use a sex-specific median split because of smaller sample sizes, as detailed below.

PLVI was measured using CT in 15 patients (78.9%) and MRI in 4 (21.1%). The modalities were considered equivalent for CSA measurement, consistent with previous PLVI studies that did not distinguish between them. The median imaging-to-pRF interval was 9 months (range, 0–176 months). A single investigator performed all psoas and L4 vertebral body CSA measurements and was not otherwise involved in the patients' clinical care or outcome assessment.

Affected-side psoas CSA was examined separately as a univariate predictor instead of the bilateral mean. Because PHN is unilateral, localized disuse atrophy ipsilateral to the symptomatic dermatome was hypothesized to be more sensitive than the bilateral average. A sensitivity analysis using bilateral mean psoas CSA is also reported in Table 1 for consistency with the PLVI definition.

Statistical methods

Continuous variables are presented as means ± standard deviations (SDs). Associations between the NRS reduction rate and candidate variables (age, sex, height, weight, body mass index [BMI], rash-to-pRF interval, comorbidities, affected-side psoas CSA, bilateral mean psoas CSA, L4 vertebral body CSA, PLVI, number of pre-pRF diagnostic blocks, and medication use) were

Table 1. Univariate correlations with NRS reduction rate

Variable	Pearson r (95% CI)	P-value	Spearman ρ	P-value
Age (yr)	−0.062 (−0.502 to 0.403)	0.800	−0.140	0.567
Sex (male = 1)	−0.459 (−0.756 to −0.006)	0.048*	−0.440	0.059
Height	−0.405 (−0.726 to 0.060)	0.085	−0.411	0.080
Weight	−0.057 (−0.498 to 0.408)	0.818	−0.147	0.547
Body mass index	0.233 (−0.247 to 0.621)	0.337	0.101	0.681
Rash-to-pRF interval	−0.241 (−0.626 to 0.240)	0.321	0.090	0.713
Hypertension	0.324 (−0.153 to 0.678)	0.177	0.252	0.297
Diabetes mellitus	0.111 (−0.362 to 0.538)	0.652	0.111	0.650
Cardiovascular disease	0.219 (−0.262 to 0.612)	0.368	0.241	0.321
Affected-side psoas CSA	−0.295 (−0.661 to 0.184)	0.220	−0.365	0.125
Bilateral mean psoas CSA	−0.305 (−0.667 to 0.174)	0.205	−0.318	0.185
L4 vertebral body CSA	−0.429 (−0.739 to 0.031)	0.067	−0.424	0.071
PLVI	−0.170 (−0.579 to 0.308)	0.488	−0.216	0.374
No. of pre-pRF blocks	−0.032 (−0.479 to 0.429)	0.897	0.104	0.671
Medication use	−0.143 (−0.561 to 0.333)	0.560	−0.161	0.510

NRS, numeric rating scale; CI, confidence interval; pRF, pulsed radiofrequency; CSA, cross-sectional area; PLVI, psoas–lumbar vertebral index.
*P<0.05.

assessed using Pearson and Spearman rank correlations. For Pearson correlation coefficients, 95% confidence intervals (CIs) were calculated using the Fisher z-transformation. Baseline medication consumption was quantified with the Medication Quantification Scale III [17]. Because PLVI differs by sex, patients were also divided into low- and high-PLVI groups using sex-specific median values (male: 0.796; female: 0.576), following previous PLVI studies in the absence of a universally accepted cutoff [1,3,5]. Between-group differences were assessed using the independent-samples t-test with Welch correction and the Mann-Whitney U test; mean differences are reported with 95% CIs. A multivariable linear regression model included the NRS reduction rate as the dependent variable and PLVI and sex as covariates to assess the PLVI–outcome association after adjustment for sex. The dependent variable was expressed in percentage points, consistent with its definition under Variables. In a sensitivity analysis, PLVI was standardized as a within-sex z-score and the regression was repeated to assess potential confounding of the raw PLVI–outcome association by sex-related differences in body size. A supplementary responder analysis compared the proportions achieving ≥30% and ≥50% NRS reductions between the low- and high-PLVI groups using Fisher's exact test. A 2-sided P-value <0.05 was considered statistically significant. All analyses were performed using R ver. 4.3.3 (R Foundation for Statistical Computing).

Results

Participants

Nineteen patients (10 women and 9 men) formed the analytic sample. Their mean age was 75.7±8.6 years, mean BMI was 23.4±3.1 kg/m^2, and mean PLVI was 0.7±0.2 (Table 2).

Main results

NRS scores decreased from 4.8±1.7 at baseline to 3.2±1.7 at 1 month. The mean absolute reduction was 1.6±2.0 points, and the mean reduction rate was 29.3%±34.0% (Table 2).

Sex was the only variable significantly associated with the NRS reduction rate in univariate analysis (Pearson r=−0.459; 95% CI, −0.756 to −0.006; P=0.048); the mean reduction rate was greater in women (43.7%) than in men (13.3%; Welch t-test, P=0.051). L4 vertebral body CSA showed a nonsignificant trend toward an association (r=−0.429; 95% CI, −0.739–0.031; P=0.067). PLVI was not significantly correlated with the NRS reduction rate (Pearson r=−0.17; 95% CI, −0.58–0.31; P=0.49; Spearman ρ=−0.22, P=0.37). Substituting bilateral mean psoas CSA for affected-side CSA in a sensitivity analysis produced a materially similar nonsignificant result (r=−0.31; 95% CI, −0.67 to 0.17; P=0.21). No other variable reached statistical significance (Table 1, Fig. 1).

Table 2. Baseline characteristics of the study population (n=19)

Characteristic	Value
Age (yr)	75.7±8.6
Sex	
Male	9
Female	10
Height (cm)	160.2±8.8
Weight (kg)	60.2±10.4
Body mass index (kg/m^2)	23.4±3.1
Rash-to-pRF interval (mo)	15.2±22.6
Hypertension	6 (31.6)
Diabetes mellitus	2 (10.5)
Cardiovascular disease	1 (5.3)
Imaging modality for PLVI	
Computed tomography	15 (78.9)
Magnetic resonance imaging	4 (21.1)
Imaging-to-pRF interval (mo)	9 (0–176)
PLVI	0.7±0.2
Baseline NRS score	4.8±1.7
NRS score at 1 month	3.2±1.7
NRS reduction (points)	1.6±2.0
NRS reduction rate (%)	29.3±34.0

Values are presented as mean±standard deviation, number, number (%), or median (range).
pRF, pulsed radiofrequency; PLVI, psoas–lumbar vertebral index; NRS, numeric rating scale.

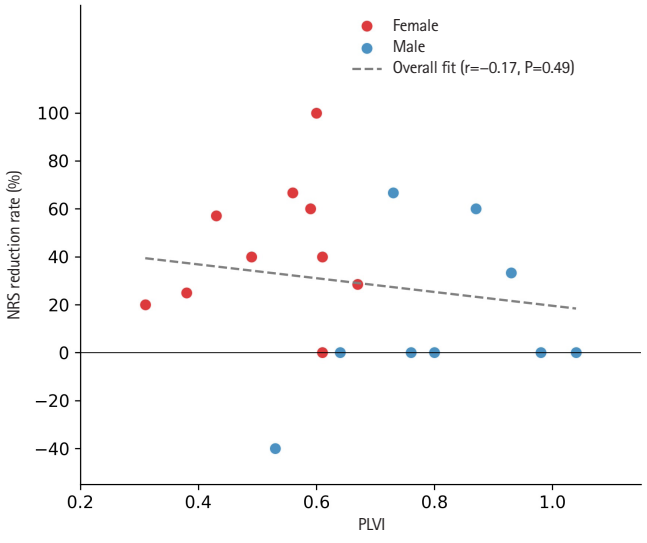


Fig. 1. Scatter plot of psoas–lumbar vertebral index (PLVI) versus numeric rating scale (NRS) reduction rate (%), stratified by sex. The dashed line shows the overall linear regression fit, which was not statistically significant.

Table 3. Comparison of NRS reduction between low- and high-PLVI groups defined using sex-specific median cutoffs

Group	NRS reduction (points)	NRS reduction rate (%)	Mean difference (95% CI)
Low PLVI (n = 9)	1.56 ± 1.51	26.2 ± 39.1	Reference
High PLVI (n = 10)	1.60 ± 2.55	32.2 ± 30.0	+6.0 (−27.9 to 39.9)
P-value (t-test)	0.963	0.712	
P-value (Mann-Whitney U test)	0.967	0.934	

The mean difference in NRS reduction rate is calculated as high minus low PLVI.
NRS, numeric rating scale; PLVI, psoas–lumbar vertebral index; CI, confidence interval.

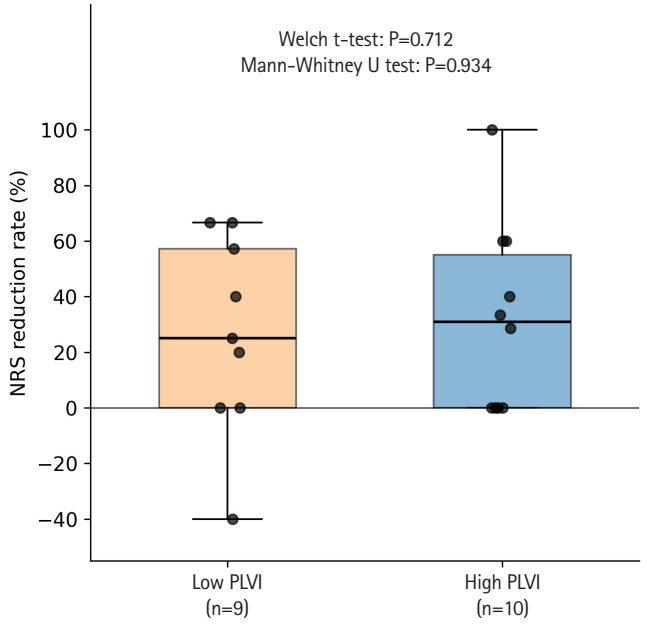


Fig. 2. Box plots of numeric rating scale (NRS) reduction rate (%) by psoas–lumbar vertebral index (PLVI) group, defined using sex-specific median cutoffs. Jittered points show individual patient values. The P-values for the Welch t-test and Mann-Whitney U test are shown.

After division into low- and high-PLVI groups using sex-specific median cutoffs, patients had similar absolute NRS reductions (low: 1.56 ± 1.51 points vs. high: 1.60 ± 2.55 points; P = 0.963) and reduction rates (low: 26.2% ± 39.1% vs. high: 32.2% ± 30.0%; mean difference, +6.0 percentage points; 95% CI, −27.9 to 39.9; P = 0.712 and P = 0.934 for the t-test and Mann-Whitney U test, respectively) (Table 3, Fig. 2). The supplementary responder analysis likewise showed no significant difference between the low- and high-PLVI groups at either the ≥ 30% threshold (4/9 [44.4%] vs. 5/10 [50.0%]; Fisher's exact P = 1.000) or the ≥ 50% threshold (3/9 [33.3%] vs. 3/10 [30.0%]; Fisher's exact P = 1.000).

In the multivariable model adjusted for sex, PLVI remained nonsignificantly associated with the NRS reduction rate (B = 59.2 percentage points; 95% CI, −52.8 to 171.1; P = 0.28), whereas male sex remained independently associated with a lower reduction rate (B = −47.2 percentage points; 95% CI, −90.9 to −3.5; P = 0.036). The model explained 26.8% of the variance (R^2 = 0.268; adjusted R^2 = 0.177), and the overall F-test approached but did not reach significance ($F(2,16) = 2.93$, P = 0.082) (Table 4). In the sensitivity analysis using within-sex standardized PLVI to address potential confounding by sex-related body size, the PLVI association remained nonsignificant (B = 8.1 percentage points per SD; 95% CI, −7.7 to 24.0; P = 0.29), while the male-sex association remained significant (B = −30.4; 95% CI, −60.5 to −0.3; P = 0.048).

Table 4. Multivariable linear regression of NRS reduction rate on PLVI, adjusted for sex

Predictor	B (% points)	95% CI	t	P-value
Intercept	12.68	−49.6 to 75.0	0.428	0.672
PLVI	59.16	−52.8 to 171.1	1.117	0.279
Sex (male)	−47.20	−90.9 to −3.5	−2.289	0.036*

The dependent variable is the NRS reduction rate in % points, as defined in the Methods. Coefficients (B) are unstandardized. R^2=0.268; adjusted R^2=0.177; overall F(2,16)=2.93, P=0.082.
NRS, numeric rating scale; PLVI, psoas–lumbar vertebral index; CI, confidence interval.
*P<0.05.

Discussion

Key results

In this retrospective pilot study of patients with established PHN, PLVI was not significantly associated with short-term pain relief after DRG pRF in either univariate or sex-adjusted analysis.

Interpretation

This result contrasts with An et al.'s finding that low PLVI strongly and independently predicted PHN development after HZ [1]. Together, the findings suggest that PLVI may be more informative for predicting PHN development than for predicting response to a specific intervention after PHN is established. This distinction between risk prediction and treatment-response prediction has

not previously been highlighted in this literature.

This interpretation requires an important qualification: PLVI is, at best, an imperfect proxy for sarcopenia. It measures only psoas CSA relative to the L4 vertebral body, a single structural measure, whereas consensus definitions of sarcopenia require assessment of muscle strength and physical performance as well as muscle mass [18]. The null finding may therefore reflect limitations of PLVI as a measurement tool rather than a true absence of a relationship between sarcopenia and pRF outcomes. The results strictly indicate only that PLVI does not predict short-term pain relief after pRF in this cohort. Whether sarcopenia, as a broader multidimensional construct, influences the pRF response remains unknown and was not addressed here.

Sex was notably associated with the NRS reduction rate in this cohort, with women experiencing greater pain relief than men in the univariate analysis and in the model adjusted for PLVI. Female sex has been identified as a risk factor for PHN development [1], but its relationship with the response to pRF is poorly characterized. The present finding warrants caution because of the small sample and the possibility of confounding or chance findings from multiple comparisons. Height and L4 vertebral body CSA both showed nonsignificant negative trends with outcome ($r \approx -0.4$) (Table 1) and were themselves strongly correlated with male sex (height vs. male sex, $r = 0.75$, $P < 0.001$; L4 vertebral body CSA vs. male sex, $r = 0.43$, $P = 0.064$). These patterns suggest that the trends likely reflect confounding by sex-related body size rather than independent associations. Consistent with this interpretation, standardizing PLVI as a within-sex z-score to remove sex-related differences in absolute body/muscle size left its association with outcome nonsignificant but reversed the point estimate (raw PLVI $r = -0.17$ vs. sex-standardized PLVI $r = +0.23$). This further supports sex, rather than PLVI itself, as the more consistent correlate of outcome in this cohort.

The stronger association of sex than of PLVI with pRF outcomes is consistent with the finding by Schlereth et al. [9] that PHN pain severity correlated with central sensitization (allodynia), anxiety, depression, and younger age, but not with peripheral nerve fiber loss on quantitative sensory testing. Together, these observations suggest that central and psychological factors may contribute more to pain trajectories and treatment response in established PHN than peripheral musculoskeletal markers such as PLVI. However, we did not directly measure allodynia, anxiety, or depression and cannot confirm this hypothesis. Similarly, Xing et al. [8] found that the timing of supplemental analgesic initiation after HZ onset strongly predicted subsequent PHN risk. This underscores the possibility that the acute-phase pain trajectory, largely determined before pRF, carries more prognostic weight for interventional outcomes than a static structural measurement at the time of the procedure. The rash-to-pRF interval was not significantly associated with outcome in our cohort, but this comparison was likely underpowered.

Comparison with previous studies

Our null finding is broadly consistent with work in other interventional pain settings. Kim et al. [3] found that PLVI correlated significantly with a validated frailty scale in older spine surgery patients but was not independently associated with postoperative complications or length of stay after multivariate adjustment. They concluded that PLVI may reflect frailty without strongly predicting procedural outcomes [3]. Yoo and Kim [6] likewise found that psoas muscle index-defined sarcopenia was associated with slower pain improvement after radiofrequency ablation for lumbar facetogenic pain, whereas PLVI did not predict response and responder proportions did not differ significantly by sarcopenia status. In contrast, Kwon et al. [7] identified high-grade fatty infiltration of the cervical multifidus, assessed qualitatively rather than by CSA, as an independent predictor of poor response to cervical epidural steroid injection. Together with our findings, these results suggest that muscle quality (fatty infiltration), muscle group, and procedure may be more relevant than psoas CSA alone when predicting response to a particular intervention. Psoas-based indices such as PLVI may instead be more consistently linked to broader constructs, including frailty and disease risk, than to short-term procedural response.

Our modest mean NRS reduction rate (29.3%) should also be considered alongside the wider literature on pRF and other interventions for PHN, although differences in response definitions and follow-up periods limit direct comparison. In a sham-controlled trial, Ke et al. [10] reported significant reductions in visual analog scale scores after angulus costae pRF that persisted to 6 months. Luo et al. [11] reported approximately 75% responders ($\geq 50\%$ pain relief) at 6 months after thoracic nerve root coblation. Huang et al. [2] reported a total effective rate of 86.2% with DRG pRF plus gabapentin versus 70.7% with gabapentin alone, and Wang et al. [12] found significantly greater reductions in device-measured pain degree with pRF plus pharmacological therapy than with pharmacological therapy alone. Our cohort's lower average response was measured only at 1 month using a continuous reduction rate rather than a binary responder threshold. It may reflect differences in patient selection, outcome definition, or follow-up duration and does not necessarily indicate inferior treatment efficacy.

This comparison is particularly relevant to our older cohort (mean age, 75.7 ± 8.6 years), in whom pRF benefits may be less

durable. In a randomized trial limited to older patients with PHN, Sheng et al. [15] found that the effective rate after pRF fell from 63.2% at 1 day to 42.1% at 12 months, whereas short-term SCS maintained a substantially higher rate (79.3%) and lower pregabalin requirements. However, an earlier trial in a similar population found no significant difference between SCS and pRF [16], leaving their relative durability in older patients with PHN unresolved. The Korean Pain Society guidelines reflect this pattern by recommending pRF for refractory PHN and reserving SCS as an elective option after an inadequate response [14]. Our 1-month follow-up was too short to assess durability. Longer follow-up is needed to investigate whether central sarcopenia beyond that captured by PLVI contributes to an attenuated pRF response in older patients and whether these patients might preferentially benefit from SCS.

Limitations

This study has several limitations. First, the small sample limited power to detect moderate associations and increased the risk of type II error; this study alone cannot exclude a true association between PLVI and treatment response. Second, PLVI is an imperfect proxy for sarcopenia because it measures only psoas CSA, without assessing muscle strength or physical performance, both integral to consensus diagnostic criteria [18]. The study can therefore conclude only that PLVI did not predict short-term pRF outcomes, not that sarcopenia is unrelated to treatment response. Third, no universally accepted PLVI cutoff exists [1,3]. We pragmatically used sex-specific medians, but other strategies, such as quartile-based or outcome-optimized thresholds, might produce different results. Fourth, the single-center retrospective design limits generalizability and precludes causal inference. Fifth, only short-term outcomes were assessed, so the influence of sarcopenia on longer-term PHN outcomes remains unknown; other studies have followed patients for up to 6 months [2,10,11]. Sixth, PLVI was measured by one investigator who was not otherwise involved in the patients' clinical care. Formal blinding to outcomes and intra- or inter-rater reliability of CSA measurements were not assessed; this methodological limitation should be addressed in prospective work. Seventh, imaging for PLVI measurement was obtained at widely varying intervals before pRF (median, 9 months; range, 0–176 months), often for unrelated clinical indications. Muscle mass can change substantially over these intervals, particularly the longer ones, so PLVI may not accurately represent sarcopenia status at the time of pRF, potentially misclassifying the exposure. Finally, psychological and central sensitization variables, including allodynia, anxiety, and depression, which correlate with PHN pain severity [9], were unavailable for adjustment and may confound the observed associations with sex and PLVI.

Suggestions

Larger prospective multicenter studies with standardized PLVI cutoffs, comprehensive sarcopenia assessment including muscle strength and physical performance, and longer follow-up are needed to clarify whether sarcopenia influences responses to interventional PHN treatment. Using the present estimates with 80% power and a 2-sided $\alpha = 0.05$, approximately 270 patients would be required to detect a PLVI association of the observed magnitude ($r \approx -0.17$), and approximately 35 to confirm the observed sex effect ($r \approx -0.46$).

Conclusion

This small retrospective cohort showed no significant association between PLVI and short-term pain relief after pRF for PHN, contrasting with the previously reported association between PLVI and PHN development. The small sample and wide CIs mean that this finding does not establish the absence of a true association and should not be extrapolated to clinical practice. Sex had a consistent, exploratory association with outcome across analyses, but confirmation in a larger, adequately powered cohort is required before it can be interpreted predictively. PLVI measures only psoas CSA and may incompletely represent the broader construct of sarcopenia. Thus, the findings indicate that PLVI specifically did not predict short-term pRF response in this pilot cohort, but they do not establish whether sarcopenia itself influences treatment outcomes. These findings are hypothesis-generating rather than definitive.

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Authors' contribution

Conceptualization: WJK. Data curation: EC. Formal analysis: SHY, WJK. Methodology: SHY, WJK. Validation: SHY, WJK. Project administration: WJK. Funding acquisition: none. Writing–original draft: SHY. Writing–review & editing: SHY, EC, WJK. Final approval of the manuscript: all authors.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability
The data analyzed in this study are available from the corresponding author upon reasonable request.

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Supplementary materials
None.

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Case report

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Spontaneous retrobulbar hematoma on serial computed tomography and magnetic resonance imaging: a case report

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An 83-year-old woman presented with a 10-day history of sudden-onset diplopia in the left eye, with no preceding trauma or anticoagulant use. Initial orbital magnetic resonance imaging (MRI) on day 10 revealed a well-circumscribed retrobulbar lesion along the left inferior rectus muscle. The lesion showed heterogeneous T1 hyperintensity, low-to-intermediate T2 signal, and no definite solid enhancement, raising concern for a hemorrhagic orbital mass or neoplasm. Serial noncontrast computed tomography (CT) on days 20 and 49 showed progressive decreases in lesion size and attenuation. Follow-up MRI on day 180 confirmed complete spontaneous resolution, with no residual abnormality or underlying neoplasm. This case demonstrates that serial CT and MRI can guide safe conservative management of spontaneous retrobulbar hematoma and help avoid unnecessary surgery in clinically stable patients.

Keywords: Computed tomography; Hematoma; Hemorrhage; Magnetic resonance imaging; Orbit; Case reports

Introduction

Intraorbital hematoma has been associated with trauma, surgery, and systemic conditions such as coagulopathy. It may also develop secondary to underlying vascular abnormalities, including intraorbital arteriovenous or cavernous venous malformations, or to neoplasms [1-3]. Spontaneous intraorbital hematoma is a rare cause of an orbital mass and has been described as a hematoma, hematic cyst, hematocele, blood cyst, or "chocolate cyst" [4-6]. Histologically, these lesions contain blood and its degradation products, sometimes enclosed by a fibrous capsule that often lacks a true endothelial or epithelial lining [7]. Although computed tomography (CT) and magnetic resonance imaging (MRI) frequently provide the first diagnostic clues to hemorrhagic orbital lesions, their clinical and imaging features often overlap with those of other benign and malignant orbital lesions, including cavernous venous malformations, lymphangiomas with hemorrhage, and hemorrhagic tumors. Consequently, most previously reported patients have undergone surgery for definitive diagnosis or decompression. However, the natural history of spontaneous retrobulbar hematoma has rarely been characterized, and its evolution on imaging requires further description.

We report a case of spontaneous retrobulbar hematoma that initially mimicked a hemorrhagic tumor. Serial CT and MRI guided conservative management and documented spontaneous resolution without biopsy or surgical excision. The case illustrates the potential value of short-interval follow-up imaging for distinguishing hemorrhagic orbital lesions from true neoplasms in clinically stable patients and avoiding unnecessary invasive procedures.

Case presentation

Ethics statement

Our institutional review board of Ewha Womans University seoul hospital approved this retrospective study (approval no. EMCS 2026-02-055) and waived the requirement for informed consent.

Case report

An 83-year-old woman presented with sudden-onset diplopia

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in the left eye that had persisted for 10 days. She had no history of head or orbital trauma, anticoagulant or antiplatelet use, diabetes mellitus, or hypertension; her only medications were inhaled treatments for long-standing asthma. She reported no Valsalva-provoking episodes before symptom onset, including severe coughing, vomiting, straining during defecation, or heavy lifting. Laboratory testing showed normal coagulation parameters: platelet count, $182 \times 10^3/\mu L$; prothrombin time, 11.5 seconds (97.5%; international normalized ratio, 1.01); and activated partial thromboplastin time, 25.4 seconds. Ophthalmologic examination showed best-corrected visual acuity of 20/20 in both eyes and no relative afferent pupillary defect. Slit-lamp examination, intraocular pressure measurements, and fundus examination were unremarkable bilaterally, with no proptosis or eyelid swelling at presentation. Automated perimetry with a Humphrey visual field analyzer identified a small inferior altitudinal defect in the left eye; the right visual field was normal. Extraocular motility testing showed limited left-eye infraduction and left hypertropia, with a mass effect around the left inferior rectus muscle. Neurologic examination identified no additional focal deficits. Orbital MRI was performed with a 3-T unit. The protocol included axial and coronal precontrast T1-weighted images (T1WI) without fat saturation, axial T2-weighted images (T2WI), coronal fat-saturated T2WI, and fat-saturated contrast-enhanced 3-dimensional T1WI. For contrast-enhanced imaging, gadobutrol was administered intravenously at 0.1 mL/kg (Gadovist 7.5 mL; Bayer Schering Pharma).

Symptom onset was designated day 0, and the hospital visit occurred on day 10. Initial MRI on day 10 showed a well-circumscribed, oval, mass-like retrobulbar lesion along the left inferior rectus muscle. The lesion had heterogeneous, predominantly low-to-intermediate signal intensity with focal very-low-signal components on T2WI and heterogeneously high signal intensity on T1WI. Contrast-enhanced 3-dimensional T1WI showed no discernible solid internal enhancement (Fig. 1A). The T1 hyperintensity and heterogeneous low T2 signal initially favored a benign orbital mass with recent hemorrhage, such as a cavernous venous malformation or schwannoma, over a purely solid neoplasm or pure hematoma. Surgery was deferred because recent bleeding increased the risk of intraoperative hemorrhage, visual function was stable, and there was no optic nerve compression or orbital apex crowding. Conservative management with short-interval follow-up imaging was chosen.

The first follow-up noncontrast CT scan, obtained on day 20, showed the retrobulbar lesion in the same location. It was isoattenuating to the adjacent extraocular muscles and contained a small hyperdense component (Fig. 1B). The patient reported improvement in diplopia and less restriction of ocular movement, supporting continued observation. The second follow-up CT scan, obtained on day 49, showed marked lesion shrinkage, with only a faint soft-tissue density remaining beside the inferior rectus muscle (Fig. 1C).

Final follow-up MRI on day 180 confirmed complete lesion resolution, with no abnormal signal within or around the left inferior rectus muscle (Fig. 1D). Diplopia had almost resolved, and repeat visual field testing showed that the inferior altitudinal defect had resolved. These findings established a diagnosis of spontaneous retrobulbar hematoma that had spontaneously resorbed rather than a hemorrhagic neoplastic lesion.

Discussion

This case illustrates how serial imaging can guide the management of hemorrhagic orbital lesions and allow selected patients to avoid invasive procedures. The evolution of the imaging findings was central to the decision to continue conservative management. CT scans obtained at day 20 and day 49 showed progressive decreases in lesion size and attenuation, and MRI at day 180 confirmed complete resolution. This course strongly favored a resolving hematoma over a hemorrhagic neoplasm. Stable visual acuity and the absence of optic nerve compression at the orbital apex further supported observation. To our knowledge, most previously reported spontaneous orbital hematomas or hematic cysts were surgically confirmed, and detailed descriptions of their natural course during conservative management remain rare.

Intraorbital biopsy and surgical exploration carry risks, particularly for hemorrhagic orbital lesions, in which tissue manipulation may provoke further bleeding. Complication rates are higher than for nonhemorrhagic orbital masses [8,9], and surgery may inadvertently injure the optic nerve or extraocular muscles [10,11]. When imaging findings are consistent with blood products and there is no urgent indication for decompression, conservative management with close clinical and radiologic surveillance may therefore be reasonable. Conversely, lesion enlargement, new solid enhancing components, or evidence of orbital apex crowding or optic nerve compromise should prompt timely surgery.

Most previous reports describe patients who underwent surgery early in their course, leaving the natural history of spontaneous retrobulbar hematoma and the optimal imaging follow-up duration incompletely characterized. Our observations suggest that these hematomas may resolve over several weeks to months, apparently taking longer than the subperiosteal hematomas described previously [12]. Decisions about conservative management should be individualized through multidisciplinary assessment.

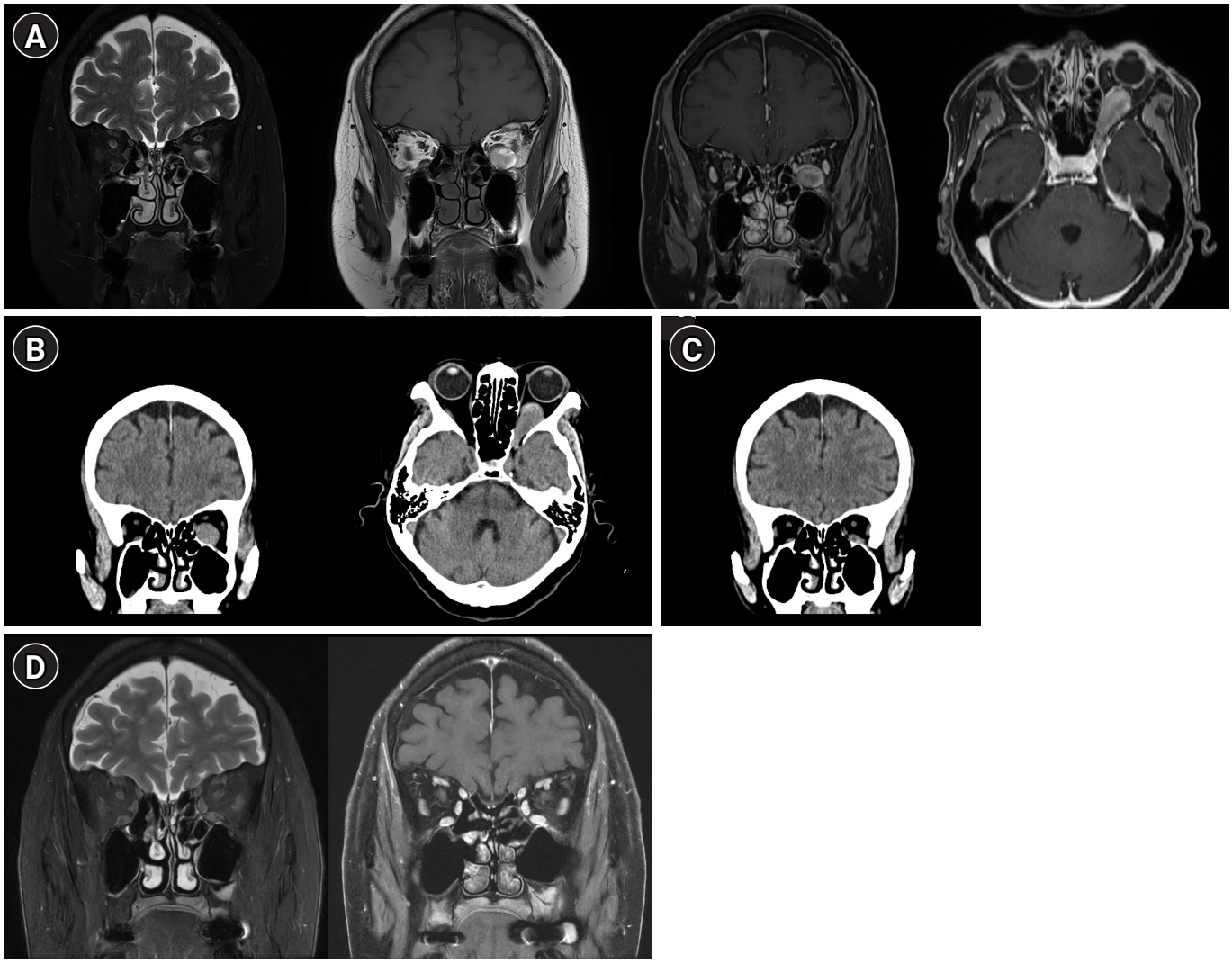


Fig. 1. Serial magnetic resonance imaging (MRI) and computed tomography (CT) findings. (A) Initial MRI on day 10. Coronal T2-weighted images (T2WI), T1-weighted images (T1WI), and contrast-enhanced coronal and axial T1WI show a well-circumscribed, mass-like retrobulbar lesion along the left inferior rectus muscle. The lesion has heterogeneous high and low signal intensity on T2WI and high signal intensity surrounding a low-to-isointense component on T1WI, without definite intralesional solid enhancement. (B) First follow-up coronal and axial CT images on day 20 show a heterogeneous iso-to-hyperdense, mass-like lesion in the left retrobulbar region. (C) Second follow-up CT on day 49 shows a marked decrease in lesion size. (D) Final MRI on day 180. Coronal T2WI and contrast-enhanced T1WI show complete lesion resolution, with no abnormal signal within or around the left inferior rectus muscle.

Hemoglobin degradation from oxyhemoglobin to deoxyhemoglobin, methemoglobin, and hemosiderin produces characteristic, stage-dependent changes in T1 and T2 signal intensity. These evolving MRI findings can help distinguish hematomas from solid vascular or neoplastic lesions [13]. Depending on the hematoma stage, however, the signal characteristics may conceal enhancing components of an underlying neoplasm. Distinguishing cavernous venous malformations from hematomas is particularly challenging. Previous studies describe marked T2 hyperintensity with internal septations, progressive centrifugal enhancement, and low-flow vascular channels in cavernous venous malformations. These features contrast with the stage-dependent layering and absence of nodular enhancement observed in hematomas [14,15]. In this patient, MRI 10 days after symptom onset showed a high-signal-intensity halo surrounding a low-to-isointense component on T1WI and layers of low and high signal intensity on T2WI, without discernible nodular enhancement. CT complemented these findings by showing decreasing lesion attenuation as blood products were resorbed, providing objective evidence of hematoma resolution. Awareness of these imaging features may help radiolo-

gists when differentiation from hemorrhagic neoplasms is difficult. Serial imaging adds temporal information that can refine the differential diagnosis and guide management.

This report has several limitations. It concerns a single patient without histopathologic confirmation because the lesion resolved spontaneously during imaging follow-up. Its primary purpose, however, was to illustrate the value of short-interval follow-up imaging when initial findings do not clearly distinguish a hemorrhagic tumor from a pure hematoma and the patient has no urgent symptoms of orbital compression. The case also demonstrates that careful imaging follow-up can be a reasonable management option for such selected patients. The 6-month follow-up was insufficient to assess long-term recurrence risk. Larger studies with longer observation are needed to determine the optimal follow-up strategy and imaging predictors of spontaneous resolution.

In this case of spontaneous retrobulbar hematoma, serial CT and MRI guided safe conservative management, and the lesion resolved spontaneously without biopsy or excision. These findings support imaging follow-up to identify patients with hemorrhagic orbital lesions who may be managed conservatively and thereby avoid unnecessary surgery when appropriately selected.

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Authors' contribution

Conceptualization: BEL. Data curation: BEL, RGY. Formal analysis: BEL, RGY. Investigation: BEL, RGY. Methodology: BEL, RGY. Validation: BEL, RGY. Writing–original draft: RGY. Writing–review and editing: BEL, RGY.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Not applicable.

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Supplementary materials

None.

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Role-play in graduate genetic counseling education: a practicum experience in South Korea

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Purpose: Clinical fieldwork in genetic counseling education is constrained by limited training sites, shortages of clinical supervisors, and administrative burdens. Simulation-based learning, including role-play, has therefore been used to support development of counseling competencies. This study described the development, implementation, operational structure, and feasibility of a role-play-based practicum in a graduate genetic counseling program.

Methods: This retrospective descriptive report was based on Genetic Counseling Practicum, a spring 2024 course for 11 third-semester students in a graduate genetic counseling program in South Korea. Twenty-two role-play scenarios were developed, including 11 hereditary cancer cases and 11 pediatric or adult genetic disorder cases. The scenarios simulated pretest and posttest encounters during a 6-week, 2-block practicum. Students alternated between counselor and counselee roles, recorded sessions outside class time, and received domain-guided peer and faculty feedback.

Results: The scenarios covered patient ages from infancy to late adulthood and included somatic and germline pathogenic variants, a negative multigene panel result, and chromosomal or epigenetic abnormalities. All 22 planned sessions were completed and recorded as scheduled, and all 11 students completed their assigned sessions. The planned assignment, recording, review, and feedback procedures were completed without documented omissions. Approximately 11 scheduled class hours were devoted to feedback, and no external clinical sites or supervisors were required.

Conclusion: This study presents an operationally feasible model for a role-play-based practicum with diverse scenarios in a graduate genetic counseling curriculum. It may serve as a practical reference for programs considering similar simulation-based training.

Keywords: Genetic counseling; Education; Role-play; Feedback

Introduction

Advances in the diagnosis and treatment of genetic disorders and hereditary cancers have made genetic counseling an increasingly important component of patient care [1-5]. Genetic counseling helps individuals and families understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease [6]. The process includes risk assessment through interpretation of family and medical histories, education about inheritance and management, and support for informed decision-making [6].

The National Society of Genetic Counselors and the Accreditation Council for Genetic Counseling have identified core competencies for genetic counseling, including professional knowledge, counseling skills, ethical judgment, and patient-centered communication [7,8]. These organizations' competency frameworks emphasize that genetic counselors are not only providers of medical information, but also healthcare professionals who address patients' emotional needs and help navigate ethical dilemmas [6,9]. Recent studies have also described competency checklists and self-efficacy measures relevant to the counseling process [10,11]. Because these competencies are difficult to cultivate through theoretical learning alone, genetic counseling programs need practice-based education that allows students to encounter diverse clinical situations repeatedly [12].

In practice, however, clinical training opportunities are limited by shortages of training institutions and qualified clinical supervisors, as well as by administrative burdens [13,14]. To address

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these constraints, the Accreditation Council for Genetic Counseling has allowed standardized patient and simulation sessions that meet specified criteria to count toward the participatory cases required for graduation [15,16].

Role-play is widely used in medical education to simulate clinical encounters and connect theoretical knowledge with practical skills [17]. In genetic counseling education, role-play may help strengthen communication skills and empathetic responsiveness by requiring learners to perform both counselor and counselee roles [18]. In South Korea, however, genetic counseling remains a relatively new formal discipline; graduate training programs and professional accreditation systems have been established only within the past decade [19]. Reports describing how role-play-based training is implemented within Korean genetic counseling programs remain scarce.

Therefore, this study aimed to describe the structure and operational procedures of a role-play-based practicum conducted within the regular curriculum of the graduate genetic counseling program at Ewha Womans University and to present an educational model for implementing role-play-based training in genetic counseling education.

Methods

Study design

This retrospective descriptive educational report examined the development, implementation, and operational feasibility of a role-play-based practicum within the regular curriculum of the graduate genetic counseling program at Ewha Womans University College of Medicine.

Educational setting and participants

The practicum was offered as the course "Genetic Counseling Practicum" during the spring 2024 semester (March–June) to 11 third-semester students. Three faculty members supervised the course by reviewing recorded sessions and providing feedback throughout the semester. In the first semester, students completed theoretical coursework in genetic counseling. In the second semester, they participated in role-play exercises in which the instructor served as the counselee and the student served as the counselor. These introductory activities focused mainly on brief explanations of inheritance patterns and genetic testing. The third-semester practicum extended this earlier training by requiring students to conduct more complete counseling encounters, respond to counselee presentations, observe peer performance, and experience both counselor and counselee roles.

Development of role-play scenarios

A total of 22 scenarios were developed to represent clinical situations encountered in genetic counseling practice: 11 hereditary cancer cases and 11 cases involving pediatric or adult genetic disorders (Table 1). Each scenario simulated either a pretest or posttest counseling session and included clinical background information needed for counseling, such as the patient's clinical presentation, family history, and genetic testing context (Table 2).

The scenarios were designed to maintain comparable difficulty within each category so that assigned cases would be reasonably equitable across students. In addition to typical genetic counseling situations, some scenarios included ethical or social issues or more challenging communication contexts.

Practicum structure and role assignment

The practicum was conducted over 6 weeks and organized into two 3-week blocks. Hereditary cancer scenarios were implemented during the first block, followed by pediatric or adult genetic disorder scenarios during the second block. This sequence was selected because hereditary cancer scenarios followed a more standardized counseling structure, whereas pediatric or adult genetic disorder scenarios involved more heterogeneous phenotypes and counseling contexts. Within each 3-week block, sessions were distributed across the weeks in a 4-4-3 pattern, for a total of 22 sessions.

Two weeks before the practicum began, students received the full list of role-play scenarios. Counselor assignments were based on students' individual case preferences, whereas counselee roles were determined by drawing lots. Because these assignment processes were independent, student pairings varied across sessions and between the hereditary cancer and pediatric or adult genetic disorder blocks rather than following a deliberately rotated pairing design. Faculty members provided patient-specific instructions individually to the students assigned to the counselee role 1 week before each session by e-mail or messenger. As a result, students assigned to the counselor role had no advance knowledge of the counselee's specific presentation.

Each role-play session was conducted outside scheduled class time by a pair of students within the assigned time frame and was recorded by the participating students. Students alternated between counselor and counselee roles; each student participated twice as a counselor and twice as a counselee during the practicum. This role-rotation structure was intended to allow students to experience both provider and patient perspectives within the genetic counseling process. Each session was scheduled for up to 30 minutes, with extensions permitted as needed to preserve the natural flow of the counseling encounter; no strict time limit was enforced. Recordings were uploaded to a shared cloud platform,

Table 1. Summary of genetic counseling role-play case scenarios

Category	Case no.	Summary
Hereditary cancer	Case 1	Pretest counseling for a 59-year-old woman with stage IV lung adenocarcinoma in whom a somatic BRCA2 variant had been identified.
	Case 2	Pretest counseling for a 52-year-old man with a family history of breast cancer.
	Case 3	Pretest counseling for a 35-year-old woman with hereditary breast cancer and a family history of a TP53 pathogenic variant.
	Case 4	Pretest counseling for a 35-year-old woman with a family history of gastric and breast cancer to evaluate the possibility of hereditary diffuse gastric cancer syndrome.
	Case 5	Posttest counseling for a 33-year-old woman with breast cancer, a family history of multiple cancers, and negative multigene panel testing results.
	Case 6	Posttest counseling for a 78-year-old woman with metastatic triple-negative breast cancer in whom a somatic BRCA1 variant had been identified and whose family history further suggested hereditary cancer.
	Case 7	Pretest counseling for a 45-year-old man with colorectal cancer and a family history of colorectal cancer to evaluate the possibility of Lynch syndrome.
	Case 8	Pretest counseling for a 28-year-old man with a clinical diagnosis of familial adenomatous polyposis.
	Case 9	Posttest counseling for a 54-year-old man with multiple colorectal adenomas and an identified heterozygous MUTYH variant.
	Case 10	Posttest counseling for a 40-year-old woman with renal cell carcinoma, pheochromocytoma, and an identified pathogenic VHL variant.
	Case 11	Posttest counseling for the family of a 15-month-old boy with retinoblastoma and an identified pathogenic RB1 variant.
Pediatric/adult genetic disorders	Case 1	Pretest counseling for a 5-year-old boy with autism spectrum disorder and developmental delay.
	Case 2	Pretest counseling for a 20-year-old woman with muscle weakness and a family history of similar symptoms to evaluate possible carrier status for Duchenne muscular dystrophy.
	Case 3	Pretest counseling for a 29-year-old woman with suspected Charcot–Marie–Tooth disease type 1A.
	Case 4	Pretest counseling for a 14-year-old boy with suspected Marfan syndrome.
	Case 5	Pretest counseling for a 2-year-old girl with rib fractures and pneumothorax to evaluate possible skeletal dysplasia.
	Case 6	Pretest counseling for a 37-year-old man with a family history of Parkinson disease.
	Case 7	Pretest counseling for an 18-month-old girl with craniofacial anomalies and a high-arched palate to evaluate possible Crouzon syndrome.
	Case 8	Posttest counseling for a newborn with characteristic facial features and cry and an identified 5p deletion consistent with cri-du-chat syndrome.
	Case 9	Posttest counseling for a 6-month-old boy with overgrowth, macroglossia, and an identified DNA methylation abnormality consistent with Beckwith–Wiedemann syndrome.
	Case 10	Posttest counseling for a 16-year-old girl presenting with amenorrhea and identified compound heterozygous CYP21A2 variants consistent with 21-hydroxylase–deficient congenital adrenal hyperplasia.
	Case 11	Posttest counseling for a 25-month-old girl with recurrent fractures, blue sclera, and an identified COL1A1 variant consistent with osteogenesis imperfecta.

where faculty members and peer students could review them before the corresponding class session and prepare feedback. The recordings were deleted after each class session and were not retained. The overall practicum workflow is summarized in Fig. 1.

Feedback process

No standardized feedback instrument, such as a fixed checklist or rating form, was used. Instead, feedback was provided in a narrative, individualized format guided by common domains: communication strategies, delivery of genetic information, empathy and responsiveness, strengths of the counseling process, and areas for improvement. Faculty members and peers reviewed the recorded sessions before the corresponding class and prepared feedback tailored to the clinical background and counseling context of each scenario (Table 2).

Class time was devoted exclusively to feedback, with approximately 30 minutes allotted to each session. Faculty members and observing peers provided comments, while the students who had performed the counselor and counselee roles reflected on their experiences and considered questions that could have been explored further from the patient's perspective. Faculty feedback synthesized key observations raised by peers and provided additional guidance on adapting communication strategies and explanations to the disease context and counseling situation.

Table 2. Representative case scenarios and patient instructions for hereditary cancer and pediatric genetic disorder cases

	Scenario	Patient role guidance
Hereditary cancer: pretest counseling	A 45-year-old man was recently diagnosed with colorectal cancer and referred to the cancer center. The referral letter indicated that multiple family members had colorectal cancer. Given his young age at diagnosis, Lynch syndrome was suspected. IHC analysis of the colorectal tumor demonstrated normal expression of MLH1, MSH2, MSH6, and PMS2 proteins. The counseling session addressed family history, personal medical history, the possibility of Lynch syndrome, testing options, and follow-up management depending on the results.	• Patient issue: The patient developed colorectal cancer at a young age and, given the family history, is concerned about the possibility of cancer in his children. The patient has 2 children: a 10-year-old son and a 12-year-old daughter.
	Counseling should include discussion of Lynch syndrome risk based on the combination of family history and IHC findings.	• Family history: Both parents are alive in their mid-70s and have no history of cancer. The paternal grandmother was diagnosed with colorectal cancer in her 70s, was treated successfully, and died of natural causes in her late 80s. The paternal great-grandfather also had colorectal cancer, with an estimated age at onset in his 60s; he died in his mid-60s. No other family history of cancer was reported.
Pediatric genetic disorders: posttest counseling	A 6-month-old boy presented with macrosomia, macroglossia, diastasis recti, an ear pit, and advanced bone age corresponding to 9 months at 6 months of chronological age. Beckwith–Wiedemann syndrome was suspected. DNA methylation testing of the 11p15.5 region revealed loss of methylation at IC2 on the maternal allele. The session was conducted as posttest counseling. The parents initially understood the test to be a genetic sequencing test and did not realize that it was a methylation assay.	• Clinical course: The child was noted to be large at birth with macroglossia, for which genetic testing was recommended and performed.
		• Pregnancy history: Natural conception, G3P1, with 1 early miscarriage. At 2–3 weeks' gestation, the mother underwent a dental X-ray, which the physician explained was harmless. Prenatal ultrasounds showed no abnormalities, but from 20 weeks' gestation, the fetus measured larger than expected for gestational age. Noninvasive prenatal testing yielded normal results; amniocentesis was not performed.
		• Birth history: The child was delivered by cesarean section when the mother was 36 years old and the father was 39 years old. Birth weight was 4.4 kg, and birth length was 53 cm.
		• Development: The child achieved head control at 2.5 months and rolled over at 3–4 months; he is currently able to sit briefly for 2–3 seconds. The child is cared for at home.
		• Physical findings: Height and weight are both above the 99th percentile. Radiographic bone age is consistent with 9 months. Diastasis recti is under observation. An ear pit is present and is also seen in the mother.
		• Family history: No additional notable findings were reported.

IHC, immunohistochemistry.

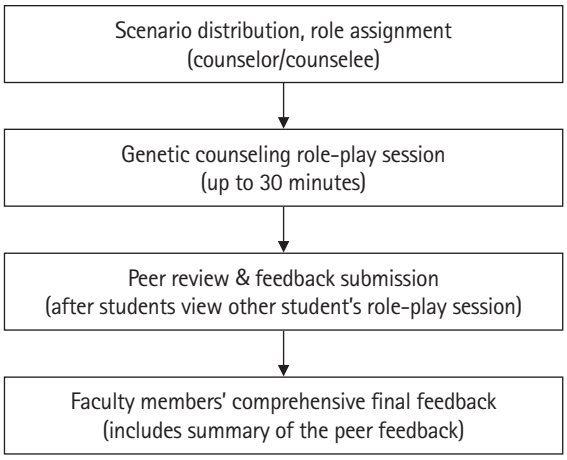


Fig. 1. Workflow for role-play implementation.

Assessment of operational feasibility

For this retrospective report, operational feasibility was characterized descriptively using aggregate course records and scheduling information available at the time of manuscript preparation. The examined indicators were completion of the planned role-play sessions; adherence to the 6-week schedule, 2-block sequence, and planned role assignments; completion of session recording, upload, advance review, and feedback; scheduled class time required for feedback; and need for external clinical training sites or external supervisors. Feasibility thresholds were not defined prospectively, and no validated implementation measure was used. Student acceptability and educational effectiveness were outside the scope of this report.

Ethical considerations

This study described the structure and operational procedures of a regular graduate-level course in the Genetic Counseling Program. No identifiable personal information or individual-level student data were collected or analyzed. The role-play recordings used for feedback preparation were deleted after each class session and were not retained beyond the practicum. Because the study was a retrospective descriptive report of a completed course, review by the Institutional Review Board (IRB) was sought after the practicum had ended, at the time of manuscript preparation. The IRB of Ewha Womans University reviewed the study and determined that it was exempt from IRB review (IRB no. 2026-0078).

Results

The 22 scenarios covered patient ages from infancy to late adulthood and included both pretest and posttest counseling situations within each category (Table 1). The hereditary cancer scenarios included diverse variant and test-result types, including somatic and germline pathogenic variants and a negative multigene panel result. The pediatric or adult genetic disorder scenarios included classic single-gene conditions as well as chromosomal or epigenetic abnormalities, representing a range of clinical situations encountered in genetic counseling practice.

All 22 planned role-play sessions were completed and recorded during the scheduled 6-week practicum, and all 11 students completed their assigned sessions. The planned assignment, recording, review, and feedback procedures were completed for all 22 sessions. Approximately 11 scheduled class hours were devoted to feedback across the 22 sessions. Faculty and peer feedback was provided for every session, and no session was omitted from the feedback process. The practicum did not require external clinical training sites or external supervisors. Time spent by faculty members and students reviewing recordings outside class was not systematically measured.

Discussion

This study described the structure and implementation of a student-led, role-play-based practicum conducted within a graduate genetic counseling program and presented an operational model used in an actual training setting. Genetic counseling requires more than the delivery of medical information; it also requires effective communication, empathetic responses, and ethical decision-making that accounts for patients' individual circumstances and values. These competencies are widely recognized as core components of genetic counseling practice [7-9]. Because such competencies are difficult to develop through theoretical instruction alone, health professional education has increasingly emphasized practice-based approaches that allow students to engage in simulated counseling situations [12,15,16,20-23]. The practicum described in this study incorporated repeated participation in simulated counseling encounters, rotation between counselor and counselee roles, and domain-guided feedback, thereby creating opportunities for experiential and reflective learning.

In this practicum, students alternated between counselor and counselee roles, with the counselee role assigned as frequently as the counselor role. This design treated the patient perspective as a central component of training rather than as a secondary activity. Beyond practicing counseling delivery, students were expected to consider how patients receive, interpret, and respond to information during counseling encounters. This experience may help future counselors judge which information to emphasize, which details to condense, and how to communicate in a patient-centered

manner [24-28]. Previous studies have similarly reported that role-switching activities in medical and communication training can promote empathy and improve understanding of patient perspectives [27,28].

Another important aspect of this practicum was the use of role-play scenarios that represented a wide range of counseling situations, including ethical or social issues as well as more typical counseling contexts. This broad scenario set exposed students to situations that may arise in actual genetic counseling practice. Case-based learning with such scenarios allows students to anticipate and practice counseling strategies for varied clinical situations that may occur in real-world practice [18,21,24]. Genetic counseling involves complex interactions shaped by disease characteristics, family relationships, and patients' personal values [6,9]. Exposure to diverse scenarios may therefore help students develop flexible counseling approaches that can be adapted to different clinical situations [29].

A distinctive feature of the practicum was its combination of peer feedback, faculty feedback, and student self-reflection. Students reviewed recordings of their peers' role-play sessions and provided peer feedback, while students who had performed the counselor and counselee roles reflected on their own experiences. This combination of peer observation, external feedback, and self-reflection encouraged students to review their counseling performance from multiple perspectives and to identify potential areas for improvement through reflective learning [30-33].

Faculty feedback was another key educational component of the practicum. Faculty members reviewed the recorded role-play sessions and peer feedback and then provided domain-guided feedback focused on competencies required in genetic counseling practice. These competencies included communication strategies, delivery of genetic information, empathetic responses, and explanation of genetic information in relation to the disease context and counseling situation. Previous studies have emphasized that feedback is a critical component of simulation-based education because it facilitates reflective learning and supports clinical skill development [30,32-34]. Similarly, the educational structure implemented in this practicum brought together role-play participation, peer observation, and faculty feedback as mutually reinforcing components of reflective learning.

This study contributes to the literature by systematically describing the structure and implementation of a role-play-based practicum conducted within an actual graduate genetic counseling curriculum. Reports describing the operational structure of role-play-based training programs in genetic counseling education remain limited. The present study therefore provides a practical example of how such sessions can be organized within a genetic counseling training program, including scenario sequencing, session scheduling, role assignment, recording procedures, and the use of feedback sessions to accommodate limited class time. Given ongoing constraints on clinical placement opportunities and supervision resources in genetic counseling education, this operational model may help programs plan simulation-based learning within their available resources.

This study has several limitations. First, it was a retrospective descriptive report of a single course conducted within 1 graduate program and 1 student cohort, which limits its generalizability to programs with different curricular structures, cohort sizes, or faculty resources. Second, operational feasibility was characterized retrospectively from available course records rather than assessed using prospectively defined criteria or a validated implementation measure. Third, faculty preparation time, student workload outside class, technical difficulties, and administrative burden were not systematically measured. Fourth, student acceptability, satisfaction, and educational outcomes, including changes in counseling knowledge, communication skills, empathy, or clinical competence, were not evaluated qualitatively or quantitatively. Finally, implementation across multiple cohorts and the long-term sustainability of the model remain unknown. Future studies should incorporate structured measures of educational outcomes, participant experience, resource use, and implementation outcomes in different training settings.

In conclusion, this study presents a detailed operational example of a role-play-based practicum implemented within a graduate genetic counseling curriculum. The model combined diverse counseling scenarios, equal rotation between counselor and counselee roles, recorded peer observation, self-reflection, and faculty feedback without requiring external clinical training sites. Although educational effectiveness, acceptability, and long-term sustainability were not evaluated, the operational structure and practical considerations described here may provide a starting point for programs designing simulation-based training within their available resources.

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Conception and design: AK, JH. Curriculum analysis: SAL, MSP. Writing–original draft: SAL. Writing–review & editing: AK, JH. Final approval of the version to be published: AK, JH.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Not applicable.

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Supplementary materials

None.

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