Technische Universität München
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A multisource approach to evaluating associated factors and disease burden of herpes zoster and postherpetic neuralgia – STOPZOS

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Table of Contents

Abbreviations

AIC: Akaike information criterion

AIDS: acquired immunodeficiency syndrome

aOR: adjusted odds ratio

CI: confidence interval

CIUS: Compulsive Internet Use Scale

COVID-19: coronavirus disease 2019

EMR: electronic medical record

GAD: generalized anxiety disorder

GAD-7: Generalized Anxiety Disorder 7

GP: general practitioner

HIV: human immunodeficiency virus

HRQoL: health-related quality of life

HZ: herpes zoster

HZAE: herpes zoster associated encephalitis

HZO: herpes zoster ophthalmicus

ICD-10-GM: International Classification of Disease (10^{th} revision) German Modification

IQR: interquartile range

IV: intravenous

NPSI: Neuropathic Pain Symptom Inventory

NRS: numerical rating scale

NSAID: nonsteroidal anti-inflammatory drug

OR: odds ratio

PCR: polymerase chain reaction

PHI: postherpetic itch

PHN: postherpetic neuralgia

PO: per os

PY: person-years

QALY: quality-adjusted life years

QoL: quality of life

REDCap: Research Electronic Data Capture

SD: standard deviation

STIKO: Ständige Impfkommission (Standing Committee on Vaccination)

UV: ultraviolet

VIF: variance inflation factor

VZV: varicella zoster virus

WHO: World Health Organization

WHO-5: WHO-Five Well-Being Index

ZBPI: Zoster Brief Pain Inventory

List of Figures

List of Tables

1. Introduction

1.1. Herpes zoster

1.1.1. History and classification

Herpes zoster (HZ), also known as shingles, is an infectious disease characterized by a painful, vesicular dermatomal rash (Strommen et al., 1988). The word “herpes” has been found in texts dating back to ancient Greece and was historically used to refer to a variety of skin lesions regardless of etiology (Beswick, 1962). Herpesviruses, with an etymology related to the Greek word for “to creep” due to the spreading nature of the skin lesions the term described (Beswick, 1962), are a family of viruses that have been observed to infect mammals, birds, and reptiles (Mettenleiter et al., 2019). Nine herpesviruses are known to only infect humans (Riddell et al., 2017; Whitley, 1996): 1) herpes simplex virus type 1, 2) herpes simplex virus type 2, 3) varicella zoster virus (VZV), 4) Epstein-Barr virus, 5) cytomegalovirus, 6) human herpesvirus 6 variant A, 7) human herpesvirus 6 variant B, 8) human herpesvirus 7, and 9) Kaposi’s sarcoma-associated herpesvirus.

1.1.2. Pathophysiology and clinical features

The responsible pathogen for HZ is the VZV, a human alphaherpesvirus (Arvin, 1996). Primary infection with VZV results in chickenpox, after which the virus enters a period of dormancy in the dorsal root ganglia and extramedullary cranial nerve ganglia (Strommen et al., 1988). Such a period of dormancy is typical for herpesviruses (Mettenleiter et al., 2019). HZ is triggered by a reactivation of VZV in sensory ganglia, which researchers attribute to a reduction of T-cell-mediated immunity (Weinberg & Levin, 2010). The characteristic dermatomal rash of the disease is caused by the transportation of reactivated VZV to epithelial cells via microtubules in axons of a sensory nerve (Gershon et al., 2010).

The course of disease for HZ can be divided into a prodromal, acute, and chronic phase (Strommen et al., 1988). Weinberg notes that patients frequently report pain and paresthesia in the affected areas during the prodromal phase, which begins as early as two weeks before skin lesions appear (2007). The acute phase is marked by the typical HZ skin lesions that are accompanied by pain and other symptoms like fever, headache, and nausea (Strommen et al., 1988). Skin lesions initially appear as macules and papules before turning into vesicles (Figure 1) and later pustules, with new lesions emerging over a three- to five-day period

(Cohen, 2013). After approximately a week, pustules begin drying out with crust formation, with these crusts typically falling off after three weeks (Strommen et al., 1988). While for most patients HZ symptoms resolve during the acute phase, some patients continue to experience symptoms and complications several weeks after the disease outbreak. Particularly patients 60 years and older experience complications like postherpetic neuralgia (PHN), a chronic pain syndrome (Strommen et al., 1988).

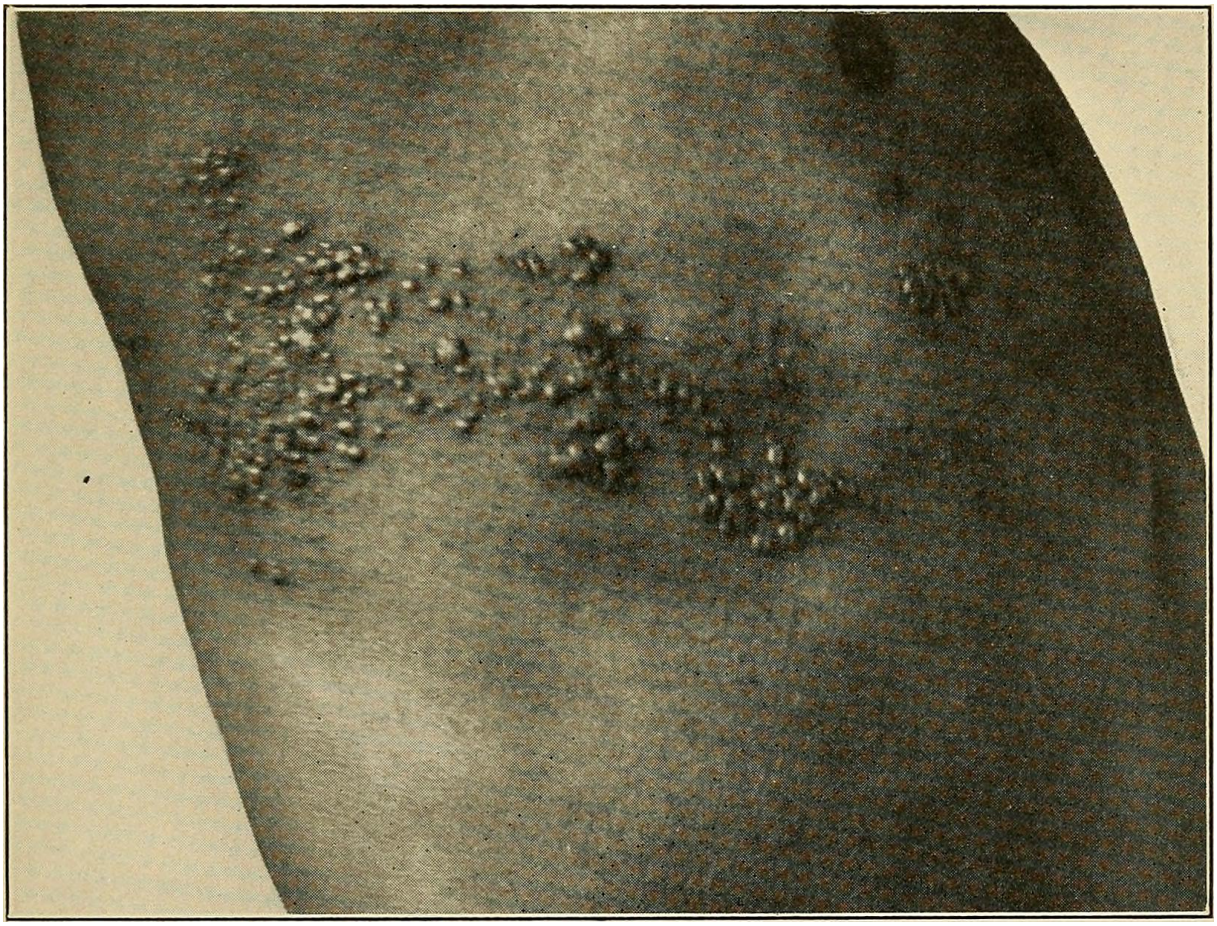


Figure 1: Thoracic herpes zoster with characteristic herpetic blisters limited to the area of a dermatome (Jelliffe & White, 1915)

Skin lesions normally do not cross the body midline and are limited to one dermatome, although they may affect two to three adjacent dermatomes (Dayan & Peleg, 2017). Percentages vary depending on the source, but the most frequently affected dermatomes in descending order are thoracic, cranial, and lumbosacral dermatomes (Figure 2) (Chidiac et al., 2001; Han et al., 1994; Hope-Simpson, 1965), with the trigeminal nerve being a common predilection site for patients with cranial involvement (Bader, 2013). Disseminated HZ, defined as the presence of more than 20 vesicles outside of the primary dermatome and those immediately adjacent, is an atypical presentation of the disease that is more frequently observed in

immunocompromised individuals (McCrary et al., 1999). In contrast, HZ can manifest without any skin rash in a condition known as zoster sine herpete, thereby complicating diagnosis (Lewis, 1958).

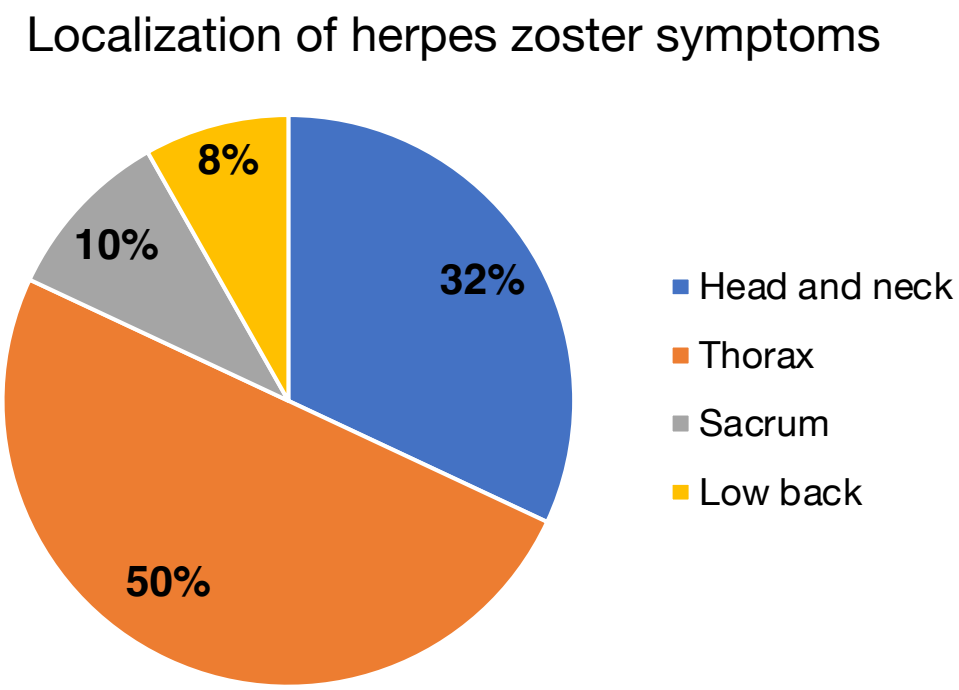


Figure 2: Distribution of predilection sites for herpes zoster symptoms among 935 participants in a study conducted by Chidiac et al., comprising patients treated by a dermatologist or general practitioner in France (2001)

1.1.3. Diagnosis

HZ is primarily a clinical diagnosis based on a characteristic distribution of skin lesions. Additional diagnostic methods can, however, confirm a suspected diagnosis in atypical presentations of HZ (Dayan & Peleg, 2017). For example, VZV antigen can be detected with direct immunofluorescence assay and VZV DNA with polymerase chain reaction (PCR) assay in cells from skin lesions, with PCR methods demonstrating a higher sensitivity and specificity (Cohen, 2013). PCR-based detection of VZV DNA in blood can be conducted for zoster sine herpete to minimize treatment delays (de Jong et al., 2001). Serological tests for the identification of VZV antibodies are possible but are less clinically relevant for diagnostics, as serological tests require more time than the other aforementioned procedures (Arvin, 1996). German guidelines suggest that the identification of IgM, IgG, and IgA VZV antibodies may be

more useful in cases where clinical symptoms are not as obvious, with significantly elevated anti-VZV IgG antibody levels in particular being indicative of HZ infection (Gross et al., 2020).

1.1.4. Therapy and prevention

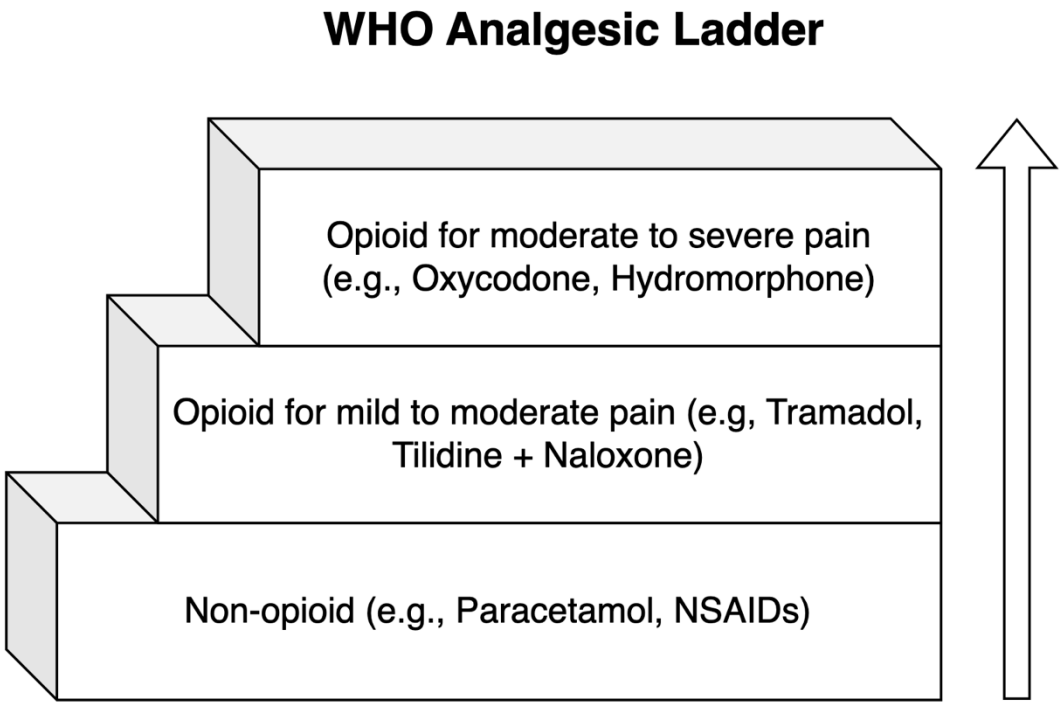
The goals of HZ treatment are to alleviate pain, shorten rash duration, and reduce the risk of disease complications (Gross et al., 2020). Although the disease is self-limiting in most cases, German treatment guidelines recommend systemic antiviral therapy for patients with an increased risk for complications, which includes patients aged 50 and older, immunosuppressed patients, and patients with cranial or cervical HZ (Gross et al., 2020). Administration of oral acyclovir within 48 hours of rash onset resulted in a significant shortening of disease duration and reduction of daily pain scores (McKendrick et al., 1986). Guidelines recommend acyclovir, valacyclovir, famciclovir, or brivudine over a course of seven days (up to ten days for intravenous [IV] acyclovir) as possible antiviral treatment options (Table 1) (Gross et al., 2020). IV acyclovir should especially be considered over oral antiviral medication for older patients with cranial or cervical HZ, patients with generalized HZ, patients with involvement of the central nervous system or visceral organs, and patients with immunosuppression, among others (Gross et al., 2020).

Table 1: Summary of possible treatment options for herpes zoster according to German treatment guidelines (Gross et al., 2020)

Antiviral Drugs	Systemic Pain Killers	Topical Treatments
Valacyclovir PO	Analgesics according to WHO analgesic ladder	Capsaicin 8% patch
Acyclovir PO	Antiepileptic Drugs	Lidocaine 5% patch
Famciclovir PO	• Gabapentin	
Brivudine PO	• Pregabalin	
Acyclovir IV	Tricyclic Antidepressants	
	• Amitriptyline	
	• Nortriptyline	
	• Desipramine	
	• Maprotiline	

Abbreviations/Acronyms: IV (intravenous), PO (per os)

Pain intensity and pain quality should be assessed when planning pain treatment options to distinguish neuropathic from nociceptive pain (Gross et al., 2020). Systemic pain killers, such as non-opioid analgesics, mild opioids, or strong opioids, should be administered according to the World Health Organization (WHO) Analgesic Ladder (Figure 3), with antiepileptic drugs, like pregabalin or gabapentin, or tricyclic antidepressants as additional options for neuropathic pain (Gross et al., 2020). Topical approaches include lidocaine patches and capsaicin patches, although these should only be applied to intact skin (Cohen, 2013; Gross et al., 2020).



Abbreviations/Acronyms: NSAIDs (Nonsteroidal anti-inflammatory drugs), WHO (World Health Organization)
Figure 3: The WHO Analgesic Ladder for the treatment of herpes zoster from Gross et al. (2020) and the WHO (1996)

There are currently two vaccines on the market for HZ, a live attenuated vaccine and a recombinant vaccine (Cunningham & Levin, 2018). The older live attenuated vaccine (Zostavax) was approved in Germany in 2013, but it was not made a recommended vaccine by the Standing Committee on Vaccination (STIKO) of the Robert Koch Institute because of its reduced efficacy with increasing age and increasing time since vaccination (Siedler et al., 2017). The newer recombinant vaccine (Shingrix), approved 2018, demonstrated high efficacy regardless of age and sustained efficacy several years after vaccination (Chlibek et al., 2016;

Cunningham et al., 2016). Shingrix has since been made a recommended vaccine in Germany for individuals 60 years and older (Siedler et al., 2019).

1.2. Postherpetic neuralgia and other complications

Population-based studies report that approximately 12% of HZ patients develop a complication (Haanpää, 2017). According to Volpi, HZ complications can be divided into four categories: cutaneous, visceral, neurological, and ocular complications (Table 2) (2007). Cutaneous complications include bacterial superinfections and scarring (el Hayderi et al., 2018; Volpi, 2007). Examples of visceral complications because of disseminated infection include pneumonia and hepatitis, with complications in rare cases even manifesting as pseudo-obstructions or spasms of the colon (R. W. Johnson et al., 2015; Tribble et al., 1993). Herpes zoster ophthalmicus (HZO) has high complication rates, with up to 90% of patients with untreated HZO developing complications (Volpi, 2007). Complications of HZO include keratitis, scleritis, uveitis, and secondary glaucoma (Womack & Liesegang, 1983).

Table 2: Classification of herpes zoster complications with corresponding examples according to Volpi (2007)

Herpes zoster complication type	Examples
Cutaneous	Bacterial superinfection, cutaneous disseminated VZV infection
Visceral	Bronchitis, gastritis, hepatitis oesophagitis, septicemia
Neurological	PHN, meningo-encephalitis, cranial and peripheral nerve palsies
Ocular	Keratitis, mydriasis, scleritis, secondary glaucoma

Abbreviations/Acronyms: PHN (postherpetic neuralgia), VZV (varicella zoster virus)

With the exception of PHN, neurological complications, particularly those that extend beyond the posterior root ganglia and first-order sensory neurons, are uncommon (Chang et al., 1987). One rare neurological complication is herpes zoster associated encephalitis (HZAE) (Peterslund, 1988). Symptoms of HZAE range from fever, headache, and vomiting to psychosis, paralysis, ataxia, and seizures (Appelbaum et al., 1962). In chronic VZV encephalitis, symptoms can appear months after the initial HZ infection (Volpi, 2007). Peripheral facial nerve paralysis that is associated with HZ oticus is known as Ramsay Hunt Syndrome, which can be accompanied by hearing loss, dizziness, and loss of taste (Wagner et al., 2012; Waldman et al., 2015).

Long term complications of HZ include a higher risk of experiencing cardio- and cerebrovascular events and complications (Erskine et al., 2017). Considered part of "VZV vasculopathies" (Gilden et al., 2009), these complications can found in both immunocompetent and immunocompromised HZ patients and include cerebral aneurysms, cerebral hemorrhaging, carotid dissection, ischemic stroke (Gilden et al., 2009), coronary heart disease, and myocardial infarction (Erskine et al., 2017). Particularly individuals aged 45 years and older are at a higher risk of these complications, which Kang et al. believe to be associated with age-related arteriosclerosis (2009). The risk has been documented to be highest in the first four weeks after HZ (Wu et al., 2019). German guidelines recommend that physicians remain alert for any symptoms indicative of a possible cardio- or cerebrovascular complication when treating HZ patients (Gross et al., 2020). Recently, Curhan et al. calculated this risk to be as high as nearly 30%, with this risk remaining as long as 12 years after the initial HZ infection (2022).

Overall, the most common complication is PHN, which is typically defined as neuropathic dermatomal pain that remains at least 90 days after initial HZ skin eruptions (Johnson & Rice, 2014; Volpi, 2007). Other definitions for PHN shorten this timeframe to one month or define the disease as persistence of pain during when the rash is healing (Schmader, 2002). The risk for developing PHN is largely influenced by age, with Gauthier et al. reporting a PHN prevalence of 10.3% for patients aged 50 to 54 years and 28.9% for patients aged 80 to 84 years in a study comprising data from over 27,000 patients (2009). Moreover, a mean duration of 7.5 months for PHN was observed, but pain can last years to a lifetime (Beydoun, 1999; Gauthier et al., 2009). Currently, the only effective prevention method is prevention of the initial HZ infection through vaccination, but effective therapy of HZ can reduce the risk for developing complications like PHN (Johnson & Dworkin, 2003; Johnson & Rice, 2014). Therapy for PHN requires a multimodal approach that includes topical treatments like lidocaine patches and systemic treatments like tricyclic antidepressants, gabapentin, and pregabalin, with opioids available as third-line drugs for pain management (Johnson & Dworkin, 2003; Johnson & Rice, 2014).

1.3. Epidemiology and risk factors

1.3.1. Incidence

The annual incidence rate for HZ reported in the literature varies depending on the study location, timeframe, and study methodology (Table 3). However, the incidence rate for HZ has been on the rise, with Yawn et al. reporting an increase from 3.2 per 1,000 person-years (PY) in 1996 to 4.1 in 2001 in the United States (2007). A study analyzing administrative claims

data from 1996 to 2006 also showed an increase in HZ incidence in the United States for adults 18 years and older (Wolfson et al., 2019). Similar patterns were observed in Germany, with crude HZ incidence increasing to 4.7 per 1000 inhabitants in 2016 from 3.0 in 2006 (Zoch-Lesniak et al., 2018).

Table 3: A selection of 15 different studies from the literature that evaluated the annual incidence of herpes zoster in the general population with their corresponding country of origin, analyzed age groups, and timeframes for the collected source data

Reference	Country	Age group (years)	Timeframe	Annual incidence rate (per 1,000 persons)
MacIntyre et al. (2015)	Australia	60 - 69	October 2006 – March 2013	13.7
Li et al. (2016)	China	50+	January 2010 – December 2012	3.4
Gonzalez Chiappe et al. (2010)	France	All	January 2005 – December 2008	3.8
Schmidt-Ott et al. (2018)	Germany	50+	November 2010 – December 2014	6.7
Ultsch et al. (2011)	Germany	50+	January 2007 – December 2008	9.6
Alicino et al. (2017)	Italy	50+	January 2013 – December 2015	6.4
Toyama et al. (2009)	Japan	All	January 1997 – December 2006	4.2
Al-Dahshan et al. (2020)	Qatar	All	January 2012 – December 2017	0.2
Cebrián-Cuenca et al. (2010)	Spain	14+	December 2006 – December 2007	4.1
Kim et al. (2014)	South Korea	All	January 2011 – December 2011	10.4
Jih et al. (2009)	Taiwan	All	January 2000 – December 2006	4.9
Brisson and Edmunds (2003)	United Kingdom	All	January 1991 – December 2000	3.7
Gauthier et al. (2009)	United Kingdom	50+	January 2000 – March 2006	5.2
B. H. Johnson et al. (2015)	United States	All	January 2011 – December 2011	4.5
Kawai et al. (2016)	United States	All	January 2000 – December 2007	3.2

Like the risk of developing PHN, the HZ incidence and the risk of developing HZ are age dependent. In a cohort of patients 50 years and older, the HZ incidence was observed to

increase to 13.19 per 1,000 PY in people ≥ 90 years old from 6.21 in patients aged 50 to 54 years (Ultsch et al., 2011). The overall lifetime risk is reported to be between 25% and 50% and increases to 50% in individuals aged ≥ 80 years (R. W. Johnson et al., 2015). HZ-related death is rare, ranging in the literature from 0.017 to 0.465 per 100,000 PY and occurring primarily in patients ≥ 60 years old (Kawai et al., 2014). Age and its influence on the immune system are therefore one of the most relevant risk factors for HZ and its complications (Weinberg, 2007).

1.3.2. Risk factors

As the immune system plays a central role in HZ pathogenesis, other forms of immune decline besides increasing age are also risk factors. Examples of diseases that compromise the immune system and that thereby increase the risk for HZ, either directly or through their therapies, include human immunodeficiency virus (HIV) infection, malignancies, and autoimmune diseases (Chakravarty, 2008; Johnson et al., 2008). In a study with data from over 22,000 HZ patients, diabetes mellitus was shown to be associated with an increased risk of HZ, which is believed to be because of weakened cellular immunity or increased neuronal stress (Heymann et al., 2008). Other studies also demonstrated associations of HZ risk with thyroid hormone imbalances, asthma, and stroke (Ajavon et al., 2015; Kwon et al., 2016; Tung et al., 2020). Similar associations were seen in studies on PHN, with diabetes, asthma, autoimmune diseases, and immunosuppressive diseases like leukemia being associated with an increased risk of PHN (Forbes et al., 2016a).

The influence of lifestyle factors like smoking and alcohol consumption on the risk of developing HZ is still unclear, although studies have shown that smoking and high alcohol consumption can suppress the immune system (Schmidt et al., 2021). Dai et al. reported a reduced risk of HZ among current smokers compared to people who never smoked (2021), whereas other studies have reported no association between smoking and HZ risk (Marin et al., 2016; Schmidt et al., 2021). In one small study, individuals with HZ were more likely to be smokers (Pezer et al., 2013). Smoking has been identified as a risk factor for neurological complications (Guidetti et al., 1990) and PHN (Forbes et al., 2016a). Alcohol consumption, regardless of risk level, was not associated with HZ risk in a study conducted on a cohort of over 100,000 Danish participants, with multiple studies reporting similar findings (Schmidt et al., 2021). Few studies have been conducted on the relationship between alcohol and PHN (Forbes et al., 2016b; Parruti et al., 2010).

In a meta-analysis of 56 studies that analyzed the influence of gender on the risk of HZ, female gender was associated with an increased risk, albeit a smaller risk than the one associated with increasing age (Marra et al., 2020). Several other studies have also reported an increased risk of PHN for women (Forbes et al., 2016a; Parruti et al., 2010). Other studies observed no differences between men and women for HZ incidence (Donahue et al., 1995) and PHN risk (Wei et al., 2019).

Considering that VZV primary infections have demonstrated a cyclical seasonal pattern for incidence (Gershon et al., 2010), studies have also reported seasonal patterns for HZ incidence and an influence of climate factors on the risk of HZ. For example, Toyama et al. observed seasonal variations for VZV infections and HZ in Miyazaki Prefecture in Japan, with the number of HZ cases increasing in the summer months (2009). Ambient ultraviolet (UV) radiation and history of sunburn were associated with an increased risk of HZ (Kawai et al., 2020). However, Ragozzino et al. observed no seasonal patterns when analyzing the monthly incidence of HZ over several years (2013).

Besides age and comorbidities like diabetes and cancer (Galil et al., 1997), other predictive risk factors for PHN have been identified. Patients with PHN were observed to have a different dermatomal distribution of HZ than patients without, with lumbar HZ being less common for PHN (Ragozzino et al., 1982). Hope-Simpson stated that while disease localization did not influence the incidence of PHN, PHN with cranial involvement was associated with a longer disease duration, particularly when compared with lumbar and sacral localizations (1975). Some studies have also identified severe acute pain during the initial HZ disease as a predictive factor for PHN (Drolet et al., 2010a; Parruti et al., 2010). However, the variety of studies employing different methodologies and definitions of PHN have made a consensus on predictive risk factors for PHN challenging (Drolet et al., 2010a).

1.3.3. Burden of disease

HZ and its complications are not only responsible for a high disease burden for affected individuals but also economic burdens for healthcare systems and society as a whole. Several studies have already demonstrated an increasing incidence of HZ in different countries (Kawai et al., 2016; MacIntyre et al., 2015; Zoch-Lesniak et al., 2018), with Kawai et al. observing a rise in incidence among all age groups (2016). The burden of disease for HZ is expected to increase considering the continuously aging global population and the role of age as a risk factor for HZ and its complications (Bloom et al., 2011; Ultsch et al., 2011). Although most patients will consult a general practitioner (GP) for HZ, older patients are more likely to have

a higher number of specialist referrals (Gialloreti et al., 2010). Hospitalization rates for HZ are the highest among patients aged 80 years and older (Kawai et al., 2014). Moreover, MacIntyre et al. reported increasing hospitalization rates for patients of this age group in Australia (2015). In Italy, costs for inpatient treatment compared to outpatient treatment were more than 20 times higher for HZ and more than 5 times higher for PHN (Gialloreti et al., 2010).

Ultsch et al. estimated that HZ and PHN respectively resulted in €85 million and €20 million in costs for the German statutory health insurance system in 2010 (2013). Vaccination studies predicted with models that vaccination of 20% of the German population aged 50 years and older could prevent 336,468 HZ cases and 48,637 PHN cases when compared with no vaccination policy (Préaud et al., 2015). Studies evaluating models of the cost-effectiveness of HZ vaccines showed that vaccinations were cost-effective when individuals were vaccinated between the ages of 60 and 70, with waning cost-effectiveness with increasing age (Damm et al., 2015).

1.3.4. Quality of life

However, economic models do not always consider less tangible costs of the disease for affected individuals, such as effects on quality of life (QoL). QoL is defined as a multidimensional and subjective measure of physical, functional, emotional, and social well-being (Cella, 1994). First mentions of the concept of QoL in the literature were made in the 1960's (Karimi & Brazier, 2016), although QoL as central element of health can be found in the WHO definition of health from 1946: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (World Health Organization, 1989).

The measure of quality-adjusted life years (QALY) considers QoL and mortality, particularly when assessing the cost-effectiveness of a medical intervention (Mehrez & Gafni, 1989). Klarman et al. (1968) were some of the first researchers to consider QALYs in a cost-effective analysis of treatments for chronic kidney disease. Later, in the 1980's, the idea of health-related quality of life (HRQoL) was introduced by Kaplan and Bush (1982), and since then several definitions for HRQoL have emerged, which Karimi and Brazier (2016) argue have created a challenge in agreeing on one definition for the term. Nevertheless, these various models of health and well-being provide valuable insight into the holistic benefits of effective prevention programs and therapies.

In Germany for individuals 50 years and older, the loss of QALYs because of HZ was reported being between 3,065 and 24,094 QALYs each year (Ultsch et al., 2011). For comparison, the estimated loss of QALYs due to HZ in England and Wales was estimated to annually be

20,000, of which 17,400 QALYs were lost due to PHN (Edmunds et al., 2001). Regarding the disease burden of HZ and PHN from patient perspectives, few studies exist in the literature on this topic (Drolet et al., 2010b). However, these studies have demonstrated that patient-reported HZ pain levels were observed to have an inverse relationship with HRQoL (Gater et al., 2014; Schmader et al., 2007). Higher acute HZ pain burden, which considers pain severity and duration, was associated with worse physical, role, and social functioning and increased emotional distress (Katz et al., 2004). Drolet et al. reported that sleep, enjoyment of life, general activities, mood, and normal work were disrupted by acute HZ and that patients with PHN indicated having symptoms of anxiety and depression (2010b). HZ has been identified as a risk factor for depressive disorders in a study from Taiwan (Chen et al., 2014). Among elderly individuals, PHN has been associated with insomnia, appetite loss, and chronic fatigue (Pickering & Leplege, 2011). Overall, PHN has demonstrated to considerably negatively affect enjoyment of life (Oster et al., 2005) and QoL (Volpi et al., 2008).

1.4. Digital disease surveillance and infodemiology

1.4.1. Definition

In Germany, where 9 out of 10 people use the Internet (Koch & Frees, 2017) and Google has a market share of 95% (StatCounter, 2022), 57% of people use the internet for health-related information at least once in 12 months (European Commission, 2014). Since the advent of the coronavirus disease 2019 (COVID-19) pandemic, there has been a rise in the number of patients missing medical appointments (Wang et al., 2020). Reduced access to clinical settings, both voluntarily and involuntarily, reflects the growing relevance of alternative sources like the internet for health information.

The term infodemiology, or information epidemiology, was introduced by Eysenbach (2002), who defined it as “the science of distribution and determinants of information in an electronic medium, specifically the Internet, with the ultimate aim to inform public health and public policy” (2011). As part of the field of health informatics, infodemiology studies utilize web-based data, like social media data or data from online search engines, to analyze a wide scope of health topics (Mavragani, 2020). Web-based data can allow for the evaluation of information in real-time, which is not always feasible when analyzing data from more traditional sources like questionnaires or registries (Mavragani, 2020). Another benefit, particularly for online search queries, is that these data provide insight into individual preferences and interests that would otherwise not be publicly stated (Mavragani & Tsagarakis, 2019). The anonymous nature of web search data is especially useful for topics of a sensitive nature

(Mavragani & Ochoa, 2019). For example, studies have demonstrated correlations between online search volume related to suicide and suicide rates (Solano et al., 2016).

Infodemiology has also seen applications in surveillance of infectious diseases. For instance, Google Trends has been used to analyze search queries related to acquired immunodeficiency syndrome (AIDS) in the United States, with parallels observed between these web-based data and data from health agencies (Mavragani & Ochoa, 2018). Moreover, the recent COVID-19 pandemic has highlighted the applications of online search data in public health, with a notable increase in the number of studies related to infodemiology and COVID-19 observed during the pandemic (Springer et al., 2021). One such study demonstrated a negative correlation between online searches for “wash hands” and the spread of COVID-19 (Lin et al., 2020), underlining how web search data can support prevention policies.

1.4.2. Applications in dermatology

Data like internet search volume have also been leveraged to analyze interest, identify areas of unmet medical need, and demonstrate seasonal variability for several dermatological conditions. For example, Mick et al. (2021) found seasonal patterns for the online search volume related to atopic dermatitis, with a higher sunlight duration being associated with a lower web search volume. Seasonal patterns for search volume were also found for scabies, with higher search volume being observed in the winter months (Wu et al., 2022). For skin cancer, search volume increased during the summer months in a study from Germany (Seidl et al., 2018). A study on psoriasis found a high search interest for alternative treatment options, which the researchers hypothesized may be attributed to dissatisfaction with current treatment options (Wallnöfer et al., 2022). For sarcoidosis, a higher online search volume per 100,000 inhabitants was observed for smaller German cities than larger ones, which may reflect differences in access to specialist care (Hilker et al., 2021). The relevance of online search data in dermatology may summarized by a study that reported on dermatology being the most searched for specialty among a selection of fifteen different types of healthcare providers (Ransohoff & Sarin, 2018)

For HZ, Google search data has been used to evaluate public interest in a HZ vaccine (Berlinberg et al., 2018). In this study, Berlinberg et al. noted seasonal patterns for both keywords related to HZ vaccines as well as keywords related to HZ symptoms in the United States (2018). However, studies that use web search data to evaluate the public interest in HZ are rare, and to the best of our knowledge, no such studies exist for Germany.

2. Aims of the study

In this two-part study, data are included from both a traditional clinical setting and an internet-based data source to consider all possible individuals affected by HZ and PHN as well as to evaluate topics related to these diseases that are relevant to affected individuals in and outside of clinical settings. While data from medical records provide important clinical information, questionnaires provide valuable insight into patient perspectives that medical records data may not reflect. The inclusion of crowdsourced data like web search data support this study's multimodal and holistic approach to assessing disease burden (Kain et al., 2023). Additionally, as regional differences in healthcare access as well as demographic differences between rural and urban areas in Germany have influenced utilization of medical services (Augurzky et al., 2013), web search data may help identify regional patterns in interest and health seeking behavior.

Overall, the disease burden of HZ and PHN for both affected individuals and society underline the need for improved and targeted public awareness and prevention campaigns. To support such endeavors, the aims of this study are:

1) to evaluate the disease burden and identify associated factors for PHN using questionnaire and medical records data from patients recruited in a traditional clinical setting

2) to analyze internet search data for HZ in Germany and its sixteen federal states to evaluate public interest in HZ and relevant influential temporal and geographic factors that modify search behavior in order to assess disease burden and identify areas of unmet need (Kain et al., 2023).

3. Questionnaire and patient medical records

3.1. Materials and methods

3.1.1. Study design

Patients were recruited from the department for dermatology and allergy of the university hospital of the Technical University of Munich. All patients treated in- or outpatient for HZ between January 2016 and December 2019 were identified using diagnostic codes for HZ from electronic medical records (EMR). The code B02 – Zoster (Herpes zoster) from the 10th revision of the International Classification of Diseases German Modification (ICD-10-GM) was used to identify possible participants (Deutsches Institut für Medizinische Dokumentation und Information, 2020).

Patients aged 18 years and older with a relevant diagnostic code were then contacted by mail and provided with the study information, informed consent forms, the study questionnaire, and a prepaid return envelope. Patients were contacted by mail in July and August 2020. Data collection proceeded from the beginning of August 2020 until the end of February 2021. In addition to age, further exclusion criteria included other forms of legal incapacity and the inability to understand the written German language (Table 4).

Table 4: Inclusion and exclusion criteria for a study evaluating questionnaire and patient medical records data of participants treated for herpes zoster at a department for dermatology and allergy of a university hospital

Inclusion Criteria	Exclusion Criteria
Being aged 18 years and older	Legal incapacity (e.g., severe dementia)
In- or outpatient treatment for herpes zoster at the department for dermatology and allergy between January 2016 and December 2019	Inability to understand a German-language questionnaire
Identified as having a B02 – Zoster (Herpes zoster) diagnostic code* in EMRs	

** From the 10th revision of the International Classification of Diseases German Modification*
Abbreviations/Acronyms: EMR (electronic medical record)

Written informed consent from each participant was acquired prior to study inclusion. All study procedures were in accordance with the Declaration of Helsinki and were reviewed as well as approved by the local ethics committee of the Technical University of Munich (reference 366/20 S).

3.1.2. Questionnaires

The questionnaire was developed by two researchers collaborating with two physicians (a dermatologist and a neurology resident physician). Questions were added only after unanimous agreement from all involved parties and were pre-tested on two inpatients treated for HZ at the time. The final questionnaire consisted of the following questions and validated questionnaires:

- *Questions about demographic information*: Participants were asked about general demographic information including age, gender, marital status, the number of children they had, education level, and current employment status.

- *Zoster Brief Pain Inventory (ZBPI)*: The ZBPI is a validated disease-specific questionnaire for HZ that uses an 11-point Likert scale (0-10) to measure the worst pain in the last 24 hours, least pain in the last 24 hours, average pain in the last 24 hours, and current paint due to HZ (Coplan et al., 2004). Furthermore, the questionnaire assesses the degree to which HZ-related pain restricts daily activity using seven questions for various categories of activity (general activity, mood, walking, work, relationships with others, sleep, and enjoyment of life) (Coplan et al., 2004). The interference of daily activities was calculated using the mean interference score if at least four of the seven items were answered (Cleeland, 2009). As defined by Copan et al., PHN in this study was defined as participants reporting a "worst pain" ZBPI score of 3 or higher (2004).

- *Neuropathic Pain Symptom Inventory (NPSI)*: The validated German-language version of the NPSI was used to evaluate the degree of neuropathic pain (Sommer et al., 2011). Ten of the twelve items ask users to assess their pain in the last 24 hours on an 11-point Likert scale for various descriptors related to burning, pressure, paroxysmal pain, evoked pain (in response to touch and temperature), and paresthesia/dysesthesia (Bouhassira et al., 2004). These 10 items are summed for a total score ranging from 0 to 100, with higher values indicating higher neuropathic pain. The remaining items ask about the frequency and duration of pain attacks, with the German version of the questionnaire additionally asking users to choose one of two diagrams that best represents their pain (attacks or continuous pain) (Sommer et al., 2011).

- *Itch*: Participants were asked to assess their itch using the numerical rating scale (NRS) (Phan et al., 2012). Two items asked users to rate the strongest itch and the average itch they experienced in the last 24 hours using an 11-point Likert scale.

- *WHO-Five Well-Being Index (WHO-5)*: The WHO-5 consists of five items that measure subjective psychological well-being (Topp et al., 2015). Users are asked to rate how often they felt the emotions described in five statements, with answers ranging from "All of the time" (5 points) to "At no time" (0 points). Scores for each item were added and then multiplied by 4 for a total score ranging from 0 (worst mental possible well-being) to 100 (best possible mental well-being) (Topp et al., 2015). As the questionnaire has been used to screen for depression (Krieger et al., 2014), the WHO-5 was used in this study to identify participants with depressive symptoms.

- *Generalized Anxiety Disorder 7 (GAD-7)*: The GAD-7 was developed to evaluate the severity of generalized anxiety disorder (GAD) symptoms (Spitzer et al., 2006) and has seen applications as a screening questionnaire for GAD, panic disorder, social anxiety, and post-traumatic stress disorder (Löwe et al., 2008). The seven items of the GAD-7 ask users to rate how often they experienced symptoms of anxiety (e.g., nervousness, the inability to relax, restlessness) in the previous two weeks (Spitzer et al., 2006). Symptoms can be experienced "Not at all" (0 points) to "Nearly every day" (3 points). Scores for each question are summed for a total score ranging from 0 to 21, with cut-off scores of 5, 10, and 15 for mild, moderate, and severe anxiety, respectively (Spitzer et al., 2006).

- *Smoking*: Participants were asked how often they smoke (never, rarely, or daily). If they were former smokers or current smokers, the questionnaire asked how many years they smoked cigarettes. Former smokers were asked for the month and year they had quit smoking. Daily smokers were asked to quantify the number of packs they smoked a day. Based on findings from prior studies (Schmidt et al., 2021), participants were ultimately categorized as either nonsmokers, former smokers, non-daily smokers, or daily smokers.

- *Alcohol consumption*: Participants were asked to rate how frequently they drank alcohol (two times a month or less, two to four times a month, two to three times a week, or at least four times a week) and how many drinks they consumed each time, with one unit of alcohol defined as one bottle of beer, approximately a quarter of a bottle of wine, or one shot of liquor. In accordance with the WHO definition for "heavy episodic drinking", participants who reported consuming six or more beverages at a time were considered in this study as "binge drinkers" (Lange et al., 2017). Based on the provided answers and the tolerable upper alcohol intake levels defined by the German

Ministry of Health, participant alcohol consumption was categorized as either low risk or higher risk (Burger et al., 2004). Low risk alcohol consumption was defined as the consumption of up to seven beverages a week for women and up to fourteen beverages a week for men, with higher risk alcohol consumption being any frequency that exceeded these amounts. The CAGE questionnaire was used to screen for alcoholism, which comprises four questions that ask participants if they ever felt the need to **c**ut down drinking, felt **a**nnoyed by criticisms of their drinking, had **g**uilty feelings about drinking, and if they needed an **e**ye-opener (alcoholic beverage) first thing in the morning (Ewing, 1984). Each question answered with a yes was assigned 1 point. Two or more positive answers were indicative of having possible alcoholism (Steinweg & Worth, 1993).

- *Internet use*: The questionnaire included questions on the weekly frequency (number of days) and daily duration (number of hours) of internet use. The short Compulsive Internet Use Scale (CIUS) consists of five items that assess the possibility of internet addiction. Users are asked, for example, to rate how often they have faced difficulties in stopping internet use, how often they have been told by relatives to reduce internet use, or how often they had slept too little because of their internet use (Bischof et al., 2016). Answers range from "never" (0 points) to "very often" (4 points) for a total score that ranges from 0 to 20, with scores of 7 points or higher indicating possible internet addiction (Besser et al., 2017).

3.1.3. Inpatient medical records

For those participants who were treated inpatient, medical records data that were collected including the following:

- *Hospital discharge date*: The date when participants were discharged from the hospital after receiving inpatient treatment for HZ was recorded to estimate the time elapsed between the initial HZ infection and study participation. The number of days was calculated between the inpatient discharge date and the date of study participation, which was recorded on the signed written consent forms. This length of time was then classified as either *less than one year*, *less than two years* (but at least one), *less than three years* (but at least two), *less than four years* (but at least three), or *less than five years* (but at least four). Time elapsed since the initial HZ infection was only calculated for inpatient participants, because an inpatient discharge date was considered the more consistent time reference, as all participants would have undergone the same

treatment over a similar timeframe, which could have not been controlled for with outpatient participants.

- *EMR HZ diagnosis*: The HZ diagnoses that patients received at presentation to the clinic were noted, with a particular focus on the disease localization and the type of dermatome affected (trigeminal, ophthalmic, cervical, thoracic, lumbar, or sacral). If patients received a diagnosis of *herpes zoster generalisatus* at the time of presentation, their disease localization was categorized as "generalized".

- *Number of comorbidities*: The number of comorbidities (0, 1, 2+) was defined as the number of comorbidities recorded in EMRs starting at admission for HZ and two years thereafter from the following list – alcohol abuse, asthma, arterial hypertension, cardiac insufficiency, chronic venous insufficiency, coronary heart disease, diabetes, depression, dyslipidemia, drug abuse, heart rhythm disorders, HIV/AIDS, hypothyroidism, inflammatory bowel diseases, malignancies, metabolic syndrome, myocardial infarction, obesity, rheumatoid arthritis, systemic lupus erythematosus, and urinary tract infection.

- *Acyclovir therapy duration*: The total number of days on which patients received IV acyclovir therapy was recorded.

- *Reported maximum pain level*: Patients treated inpatient for HZ were asked every day of treatment by medical staff if they were still experiencing any pain and if so, to rate the pain severity on a scale from 1 to 10. The highest pain severity reported during inpatient treatment was noted for this study.

3.1.4. Statistical analysis

Questionnaire data were digitized using Research Electronic Data Capture (REDCap) tools (Harris et al., 2009). Data were digitized twice and then assessed for discrepancies, with corrections made based on the source data. Data from participants who did not answer the "worst pain" question of the ZBPI, which was used to determine PHN status, were excluded from analysis. Demographics data are presented as absolute and relative frequencies. Descriptive data were calculated and stratified according to PHN status for age, gender, ZBPI pain severity scores, ZBPI pain interference, the NPSI, itch severity scores, the WHO-5, the GAD-7, alcohol consumption, smoking habits, internet addiction, and inpatient medical records data.

Group differences for categorical variables were identified using chi-square tests or Fisher's exact tests if assumptions were not met. For continuous variables, the Shapiro-Wilk test and Levene's test were used to test the assumptions of normality and equal variances, respectively. As these assumptions were violated for all variables of interest, group differences were tested using the Mann-Whitney U test, with data reported as medians with interquartile ranges (IQR). Correlations between the worst pain severity and age, mental health scores, and pain-related interference in daily activities were examined using Spearman's correlation coefficient.

The data subset of complete cases of patients for whom inpatient medical records were found and who provided information for all variables of interest was used to identify associations with PHN. Univariable binomial logistic regressions were first conducted for age, gender, itch severity scores, the GAD-7, the WHO-5, smoking habits, alcohol consumption, and inpatient medical records data. Variables previously analyzed in the literature (age, gender, mental health outcome measures, smoking habits, alcohol consumption, ophthalmic nerve involvement, and acute pain severity) and variables with $p < .05$ in the univariable analyses were then included in a Firth logistic regression due to the small sample size of this subset (Puhr et al., 2017).

As the two itch severity scores being included in the same model would have likely resulted in multicollinearity, average itch and strongest itch were added to two separate regressions containing all other relevant variables, with the Akaike information criterion (AIC) of each model being used to select the model for final evaluation. Multicollinearity in the individual models was further tested with variance inflation factors (VIF). Odds ratios (OR) and adjusted odds ratios (aOR) are reported with their 95% confidence interval (CI).

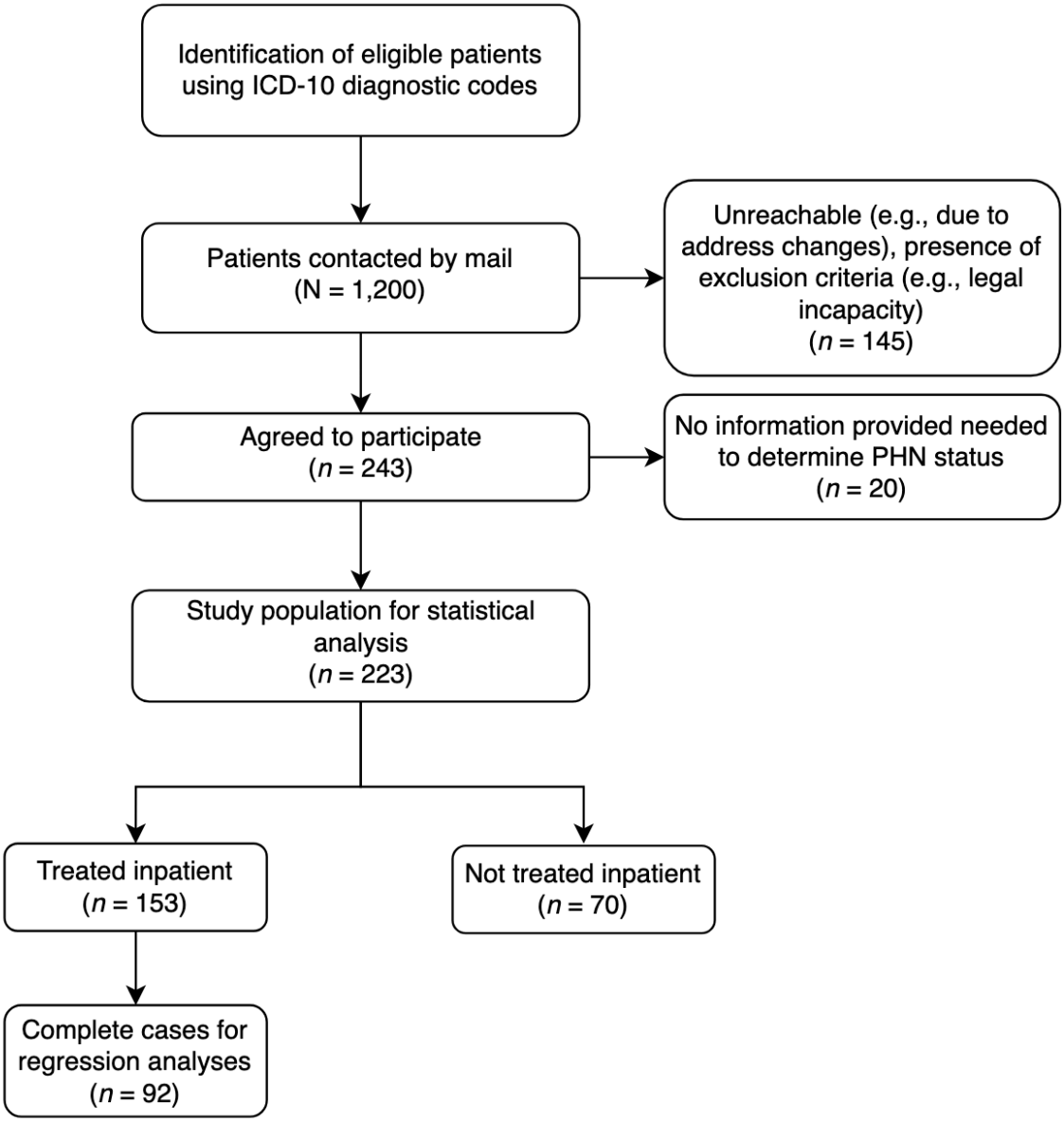
The significance level was set to .05. Data analysis was conducted using the open-source software jamovi Desktop for macOS, version 2.3 (The jamovi project, 2022) and R Statistical Software, version 4.2.2 (R Core Team, 2022), with the R package "logistf" (Heinze et al., 2022).

3.2. Results

3.2.1. Study population information

A total of 1,200 patients were contacted by mail based on diagnostic codes from EMRs, with 145 exclusions made for patients who were ineligible due to legal incapacity, who had died, or who were not reachable because of address changes (Figure 4). The response rate was

23.0% (243 respondents). Data from 20 patients were excluded from analyses, as no information to determine PHN status was provided for the ZBPI questionnaire. Overall, data from 223 participants were included in final analyses. Women comprised 51.1% of the study population (Table 5). Participants were on average 65.4 years old (± SD 16.8), with 65.5% of all participants being 60 years and older and more than half retired.



Abbreviations/Acronyms: ICD-10 (International Classification of Disease [10th revision]), PHN (postherpetic neuralgia)

Figure 4: Flowchart of the participant recruitment process with identification of participant subsets based on inpatient treatment history for herpes zoster

Table 5: General characteristics of the study population, comprising patients treated in- and outpatient for herpes zoster from January 2016 to December 2019

Characteristic	%	N
Age		
< 50 years	19.3%	43
50 - 59 years	15.2%	34
60 - 69 years	13.0%	29
70 - 79 years	29.6%	66
80+ years	22.9%	51
Average age ± SD	65.4 ± 16.8 years	
Gender		
Male	48.9%	109
Female	51.1%	114
Highest level of education		
No degree	1.8%	4
Elementary/General school (Hauptschule)	7.8%	17
Secondary school (Realschule)	8.3%	18
Secondary school (Gymnasium)	6.0%	13
Completed vocational training	31.7%	69
University of applied sciences degree	17.4%	38
University degree	27.1%	59
Missing values		5
Employment status		
Not employed	5.0%	11
Currently employed	42.7%	94
Retired	52.3%	115
Missing values		3
Marital status		
Single	22.2%	48
Married	55.6%	120
Separated	1.4%	3
Divorced	10.6%	23
Widowed	10.2%	22
Missing values		7

Abbreviations/Acronyms: SD (standard deviation)

Out of a total of 198 responses to the question “Have you had any pain caused by your shingles in the last 24 hours?” of the ZBPI, 52 participants answered “Yes” (26.3%). When inquired about the worst shingles-related pain in the last 24 hours, 26.0% (n = 58) of the 223 respondents reported pain values indicating possible PHN (Figure 5). Prevalence rates for

PHN for different age groups varied from 4.7% in participants younger than 50 years old to 37.3% in patients older than 80.

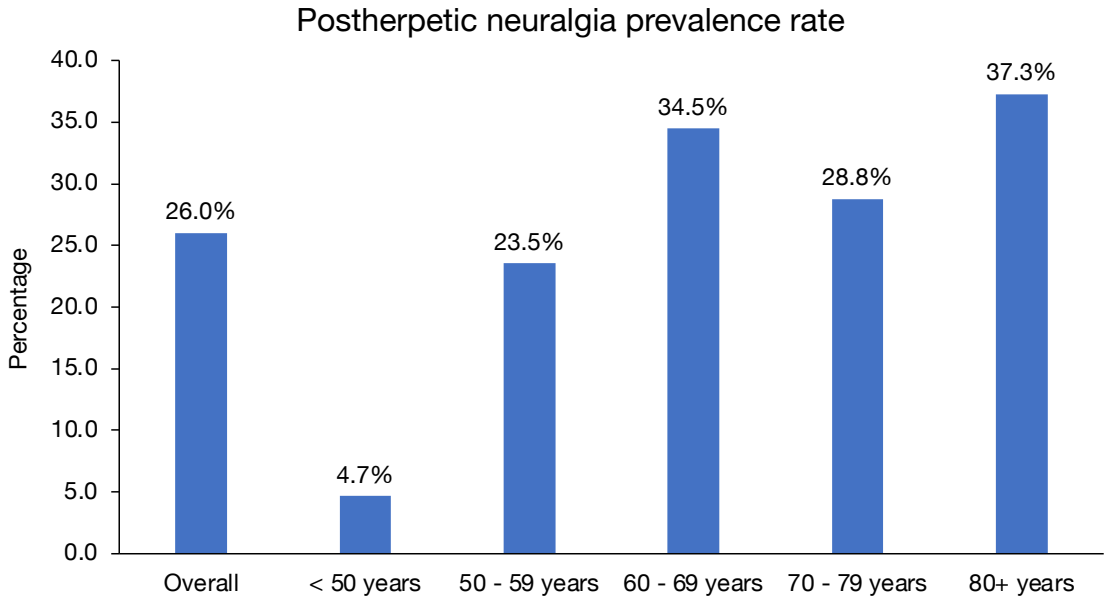


Figure 5: Postherpetic neuralgia prevalence rates for study participants overall and according to various age groups for adult participants treated in- and outpatient for herpes zoster at a dermatology department of a university hospital

3.2.2. Group differences

When stratified according to PHN status, statistically significant differences were observed for age, ZBPI pain severity scores, ZBPI pain interference, the NPSI, itch severity scores, the WHO-5, and the GAD-7 (Table 6). No differences were observed for the CAGE test, internet addiction, the duration of acyclovir therapy, and maximum reported pain during inpatient treatment. Among the categorical variables, differences were observed for the number of comorbidities, $\chi 2 = 7.32$ (2, N = 153) (Table 7).

Table 6: Results of Mann-Whitney U tests that analyzed group differences between participants with and without postherpetic neuralgia (PHN). Data from the following standardized questionnaires were included: Zoster Brief Pain Inventory (ZBPI), Neuropathic Pain Symptom Inventory (NPSI), WHO-Five Well-Being Index (WHO-5), Generalized Anxiety Disorder 7 (GAD-7), CAGE test for alcoholism, and the short Compulsive Internet Use Scale (CIUS). Furthermore, data for itch severity, duration of inpatient antiviral treatment, and maximum pain severity during inpatient treatment were also compared.

Variable	PHN	N (%)	Median	Q1	Q3	*p* value
Age	No	165 (74.0%)	68.00	50.00	76.00	< .001
	Yes	58 (26.0%)	76.00	64.25	81.00	
	Missing values	0				
ZBPI - Worst pain in the last 24 hours	No	165 (74.0%)	0.00	0.00	0.00	< .001
	Yes	58 (26.0%)	6.00	4.00	7.00	
	Missing values	0				
ZBPI - Least pain in the last 24 hours	No	163 (73.8%)	0.00	0.00	0.00	< .001
	Yes	58 (26.2%)	2.00	1.00	3.00	
	Missing values	2				
ZBPI - Average pain in the last 24 hours	No	165 (74.3%)	0.00	0.00	0.00	< .001
	Yes	57 (25.7%)	4.00	3.00	5.00	
	Missing values	1				
ZBPI - Current pain	No	164 (73.9%)	0.00	0.00	0.00	< .001
	Yes	58 (26.1%)	3.50	2.00	5.00	
	Missing values	1				
ZBPI pain interference	No	147 (72.1%)	0.00	0.00	0.00	< .001
	Yes	57 (27.9%)	2.86	1.29	4.43	
	Missing values	19				
NPSI	No	138 (75.0%)	0.00	0.00	1.75	< .001
	Yes	46 (25.0%)	27.50	18.25	43.00	
	Missing values	39				
Average itch in the last 24 hours	No	154 (73.0%)	0.00	0.00	0.00	< .001
	Yes	57 (27.0%)	3.00	2.00	5.00	
	Missing values	12				
Strongest itch in the last 24 hours	No	154 (74.4%)	0.00	0.00	0.00	< .001
	Yes	53 (25.6%)	4.00	1.00	7.00	
	Missing values	16				
WHO-5	No	150 (73.5%)	76.00	64.00	92.00	< .001
	Yes	54 (26.5%)	50.00	32.00	72.00	
	Missing values	19				
GAD-7	No	153 (73.9%)	2.00	0.00	4.00	< .001
	Yes	54 (26.1%)	5.00	3.00	9.50	
	Missing values	16				
CAGE	No	150 (75.4%)	0.00	0.00	0.00	.165
	Yes	49 (24.6%)	0.00	0.00	0.00	

Variable	PHN	N (%)	Median	Q1	Q3	*p* value
	Missing values	24				
short CIUS	No	141 (75.0%)	1.00	0.00	2.00	.516
	Yes	47 (25.0%)	1.00	0.00	2.00	
	Missing values	35				
Acyclovir therapy duration (in days)	No	114 (75.5%)	7.00	7.00	7.00	.316
	Yes	37 (24.5%)	7.00	7.00	7.00	
	Missing values	2				
Maximum pain during inpatient treatment	No	113 (75.8%)	5.00	3.00	7.00	.105
	Yes	36 (24.2%)	6.00	3.75	8.00	
	Missing values	4				

Abbreviations/Acronyms: CIUS (Compulsive Internet Use Scale), GAD-7 (Generalized Anxiety Disorder 7), NPSI (Neuropathic Pain Symptom Inventory), PHN (postherpetic neuralgia,) Q1 (lower quartile), Q3 (upper quartile), WHO-5 (WHO-Five Well-Being Index), ZBPI (Zoster Brief Pain Inventory)

Table 7: Results of chi-square and Fisher's exact tests that analyzed group differences between participants with and without postherpetic neuralgia (PHN)

Variable	PHN	N (%)	χ2	df	*p* value
Gender		223	0.04	1	.843
Male	No	80 (35.9%)			
	Yes	29 (13.0%)			
Female	No	85 (38.1%)			
	Yes	29 (13.0%)			
Smoking		214			.884*
Daily smoker	No	15 (7.0%)			
	Yes	4 (1.9%)			
Non-daily smoker	No	12 (5.6%)			
	Yes	2 (0.9%)			
Former smoker	No	34 (15.9%)			
	Yes	12 (5.6%)			
Nonsmoker	No	101 (47.2%)			
	Yes	34 (15.9%)			
Alcohol consumption risk		156	0.03	1	.862
Higher risk	No	20 (12.8%)			
	Yes	6 (3.8%)			
Low risk	No	102 (65.4%)			
	Yes	28 (17.9%)			
Alcohol binge drinking		157			.452*
Yes	No	7 (4.5%)			
	Yes	3 (1.9%)			
No	No	116 (73.9%)			
	Yes	31 (19.7%)			
Herpes zoster ophthalmicus		153	0.003	1	.959
Yes	No	57 (37.3%)			
	Yes	18 (11.8%)			
No	No	59 (38.6%)			
	Yes	19 (12.4%)			
Number of comorbidities		153	7.32	2	.026
0	No	47 (30.7%)			
	Yes	6 (3.9%)			
1	No	33 (21.6%)			
	Yes	15 (9.8%)			
2+	No	36 (23.5%)			
	Yes	16 (10.5%)			

** Fisher's exact test*
Abbreviations/Acronyms: PHN (postherpetic neuralgia)

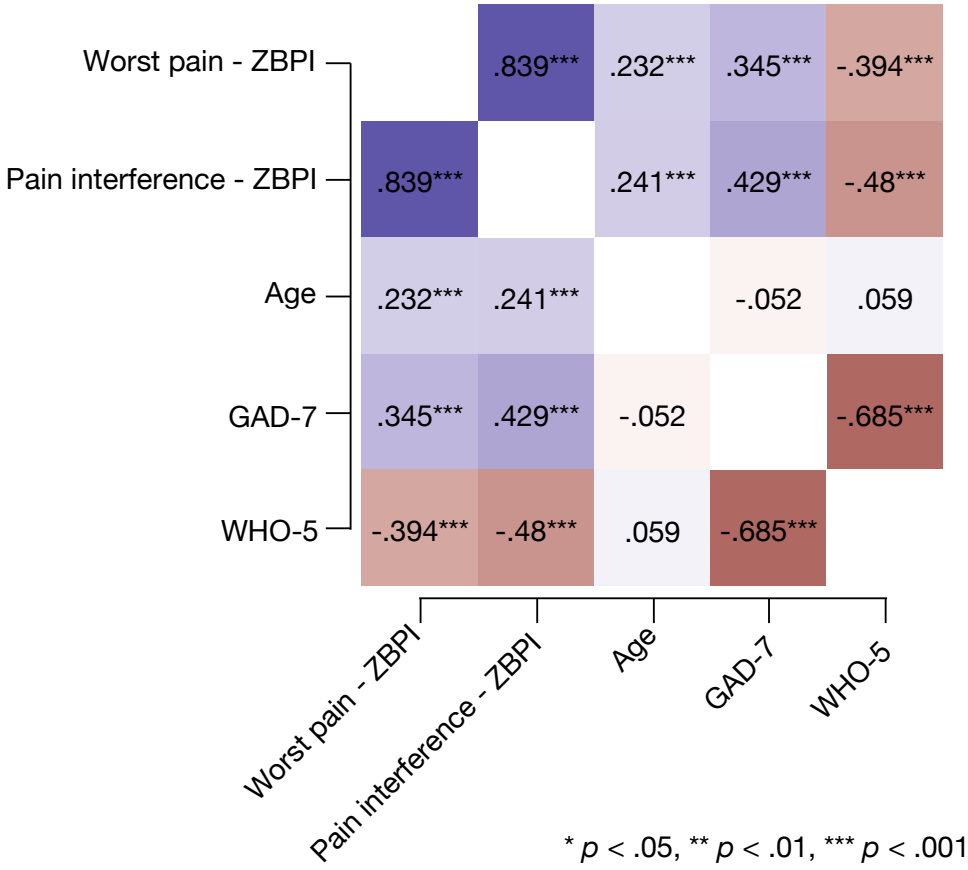
3.2.3. Correlation between worst pain severity, age, and QoL measures

A high positive correlation was observed between severity for the worst pain in the last 24 hours reported in the ZBPI and pain-related interference of daily activities (r_s = .84, p = < .001) (Table 8). A moderate positive correlation was observed between worst pain severity and GAD-7 scores for anxiety (r_s = .35, p = <.001), and a moderate negative correlation was observed between worst pain severity and WHO-5 scores for mental well-being and depression (r_s = -.39, p = <.001). A moderate positive correlation was observed between pain-related interference and age (r_s = .241, p = <.001). No notable correlations were observed between age and mental health outcomes (Figure 6).

Table 8: Spearman's correlation coefficients (r_s) for the relationship between the worst pain severity in the last 24 hours reported in the ZBPI and age, pain-related interference of daily activities, and mental health outcomes for anxiety (GAD-7) and mental well-being (WHO-5)

		Worst pain - ZBPI	Age
Pain interference - ZBPI	r_s	.84	.24
	p value	< .001	< .001
	N	204	204
GAD-7	r_s	.35	-.05
	p value	< .001	.457
	N	207	207
WHO-5	r_s	-.39	.06
	p value	< .001	.399
	N	204	204
Worst pain - ZBPI	r_s	-	.23
	p value	-	< .001
	N	-	223

Abbreviations/Acronyms: GAD-7 (Generalized Anxiety Disorder 7), WHO-5 (WHO-Five Well-Being Index), ZBPI (Zoster Brief Pain Inventory)



Abbreviations/Acronyms: GAD-7 (Generalized Anxiety Disorder 7), WHO-5 (WHO-Five Well-Being Index), ZBPI (Zoster Brief Pain Inventory)

Figure 6: Heatmap for Spearman's correlation coefficients for the relationship between the worst pain severity in the last 24 hours reported in the ZBPI and age, pain-related interference of daily activities, and mental health outcomes for anxiety (GAD-7) and mental well-being (WHO-5). Increasingly darker purple color indicates positive correlations, and increasingly darker red color indicates negative correlations

3.2.4. Overview of inpatient medical records data

Inpatient medical records data were found for 153 respondents (68.6% of the study population). Of these 153 participants, 24.2% (n = 37) reported pain levels indicative of PHN (Figure 7).

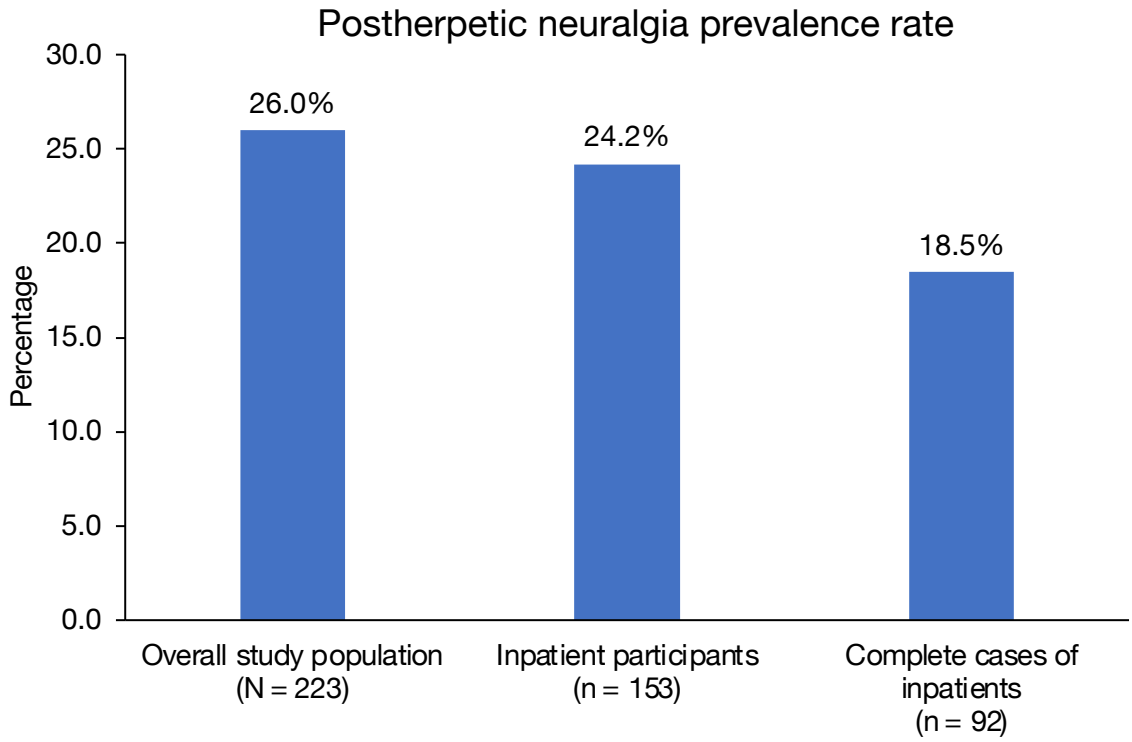


Figure 7: Postherpetic neuralgia prevalence rates of various study subset populations for adult participants treated in- and outpatient for herpes zoster at a dermatology department of a university hospital. Rates were calculated for all study participants, for only those treated inpatient, and for only those inpatient participants for whom complete cases for certain variables of interest for regression analyses were found

More than half of the participants treated inpatient (57.5%) were diagnosed with HZ with trigeminal involvement (Figure 8). Specifically, nearly all of these patients had HZO, accounting for slightly more than half of all inpatient cases (*n* = 78, 51.0%). HZ with only sacral involvement was observed for three (2.0%) of the participants who were treated inpatient.

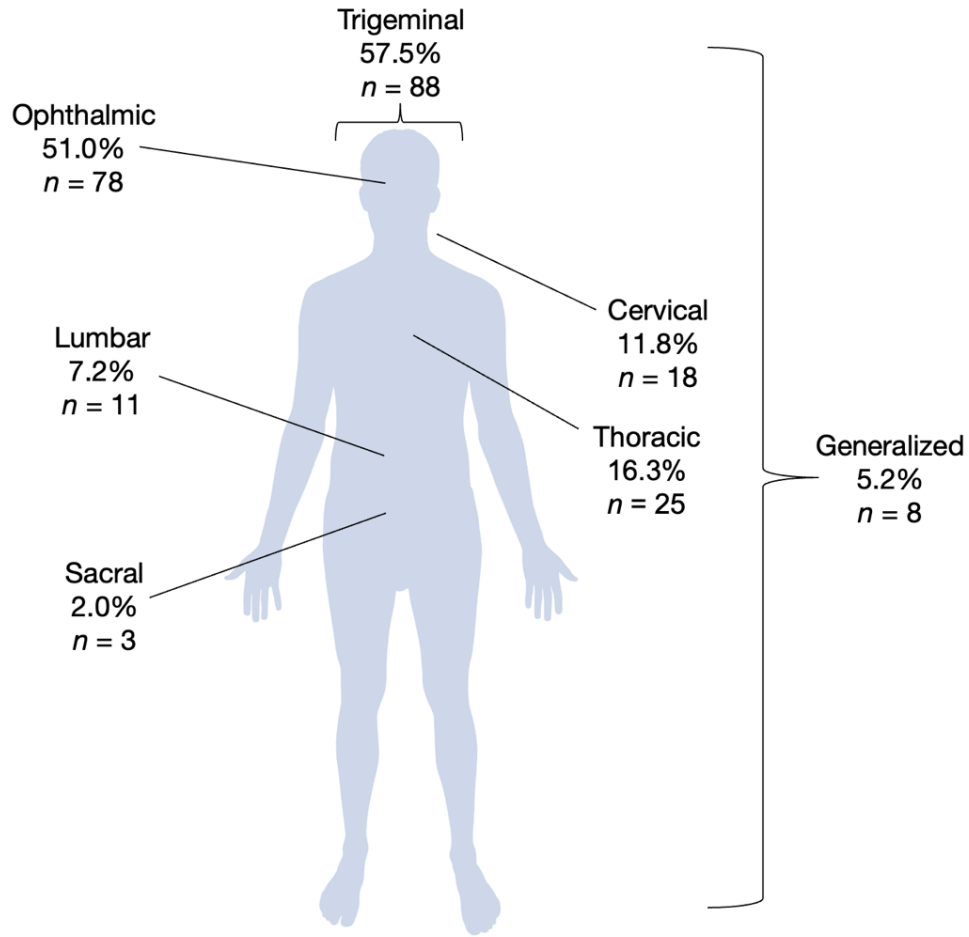


Figure 8: Frequency of herpes zoster diagnoses from electronic medical records (EMR) according to dermatome type (trigeminal, ophthalmic, cervical, thoracic, lumbar, sacral) for the subset of 153 participants treated inpatient for herpes zoster

The distribution of the time elapsed between the initial HZ infection, with the inpatient discharge date used as the reference point, and the date of study participation showed a similar pattern for all inpatient participants (Figure 9) and for only those inpatient participants reporting symptoms indicative of PHN (Figure 10). For both subsets of participants, most participants had their initial HZ infection between one and four years prior to study participation. The mean elapsed time was 2.5 years (± SD 1.2) for all inpatient participants and 2.6 years (± SD 1.3) for only those inpatient participants with PHN.

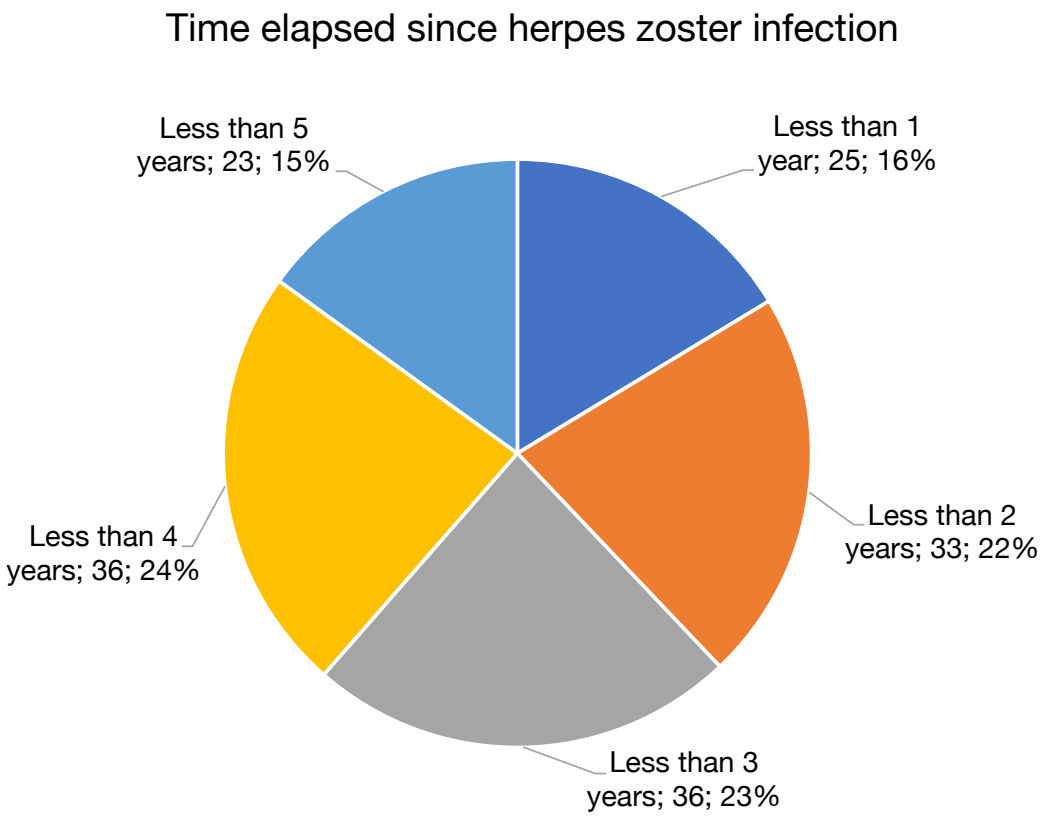


Figure 9: Pie chart of the distribution of the time elapsed between hospital discharge and questionnaire participation for a subset of participants treated inpatient for herpes zoster (*n* = 153). The elapsed time was classified as *less than one year*, *less than two years* (but at least one), *less than three years* (but at least two), *less than four years* (but at least three), or *less than five years* (but at least four). Each pie section shows the category name, the number of participants, and the percentage of the subset study population

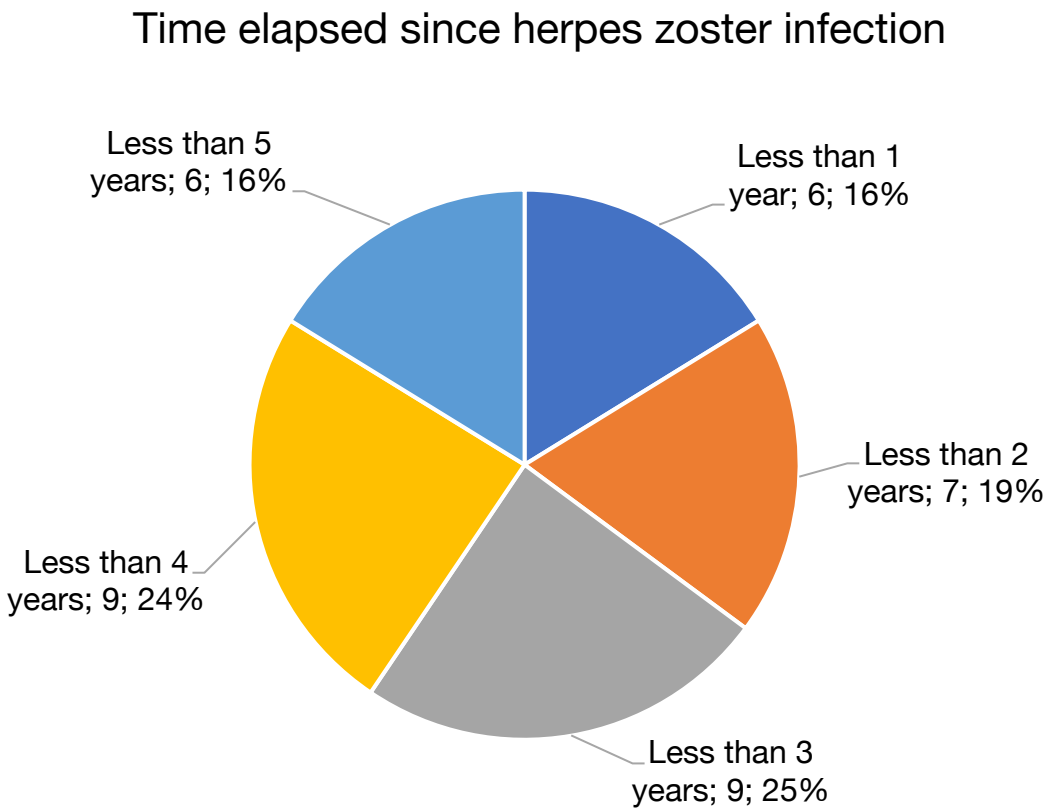
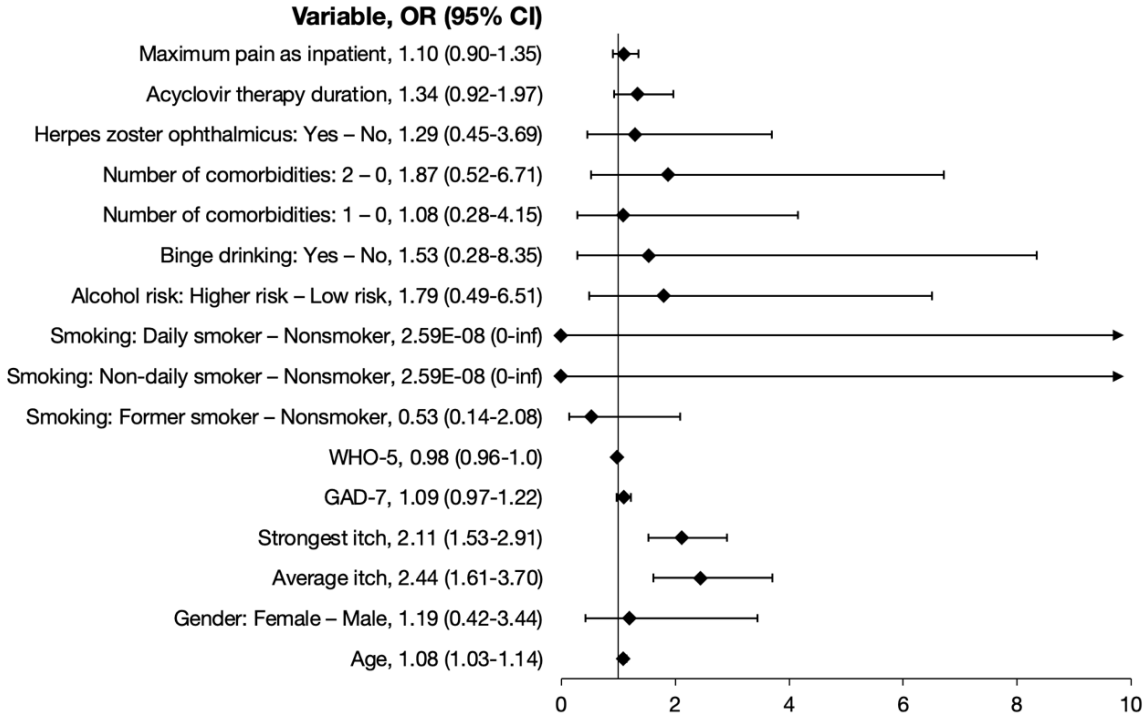


Figure 10: Pie chart of the distribution of the time elapsed between hospital discharge and questionnaire participation of a subset of participants with PHN who were treated inpatient for herpes zoster (*n* = 37). The elapsed time was classified as *less than one year*, *less than two years* (but at least one), *less than three years* (but at least two), *less than four years* (but at least three), or *less than five years* (but at least four). Each pie section shows the category name, the number of participants, and the percentage of the subset study population

3.2.5. Associations with PHN

A total of 92 complete cases were found for the variables of interest for logistic regression analyses (Figure 4). In total, 17 participants (18.5%) of these 92 participants reported pain values indicative of PHN (Figure 7). Univariable analyses showed a significant association between PHN and age (OR 1.08 [95% CI: 1.03-1.14], $p = .002$), average itch severity (OR 2.44 [1.61-3.70], $p < .001$), and strongest itch severity (OR 2.11 [1.53-2.91], $p < .001$) (Figure 11, Table 9). Two models with all variables of interest were formed using Firth logistic regressions, one that analyzed the association with strongest itch severity (AIC = 72.7) and the other with average itch severity (AIC = 73.0). The Firth regression that considered strongest itch severity was chosen as the final model, where age (aOR 1.07 [1.00-1.17], $p = .040$) and strong itch severity (aOR 1.94 [1.43-2.95], $p < .001$) were observed as a significant associated factors for PHN (Figure 12, Table 10).



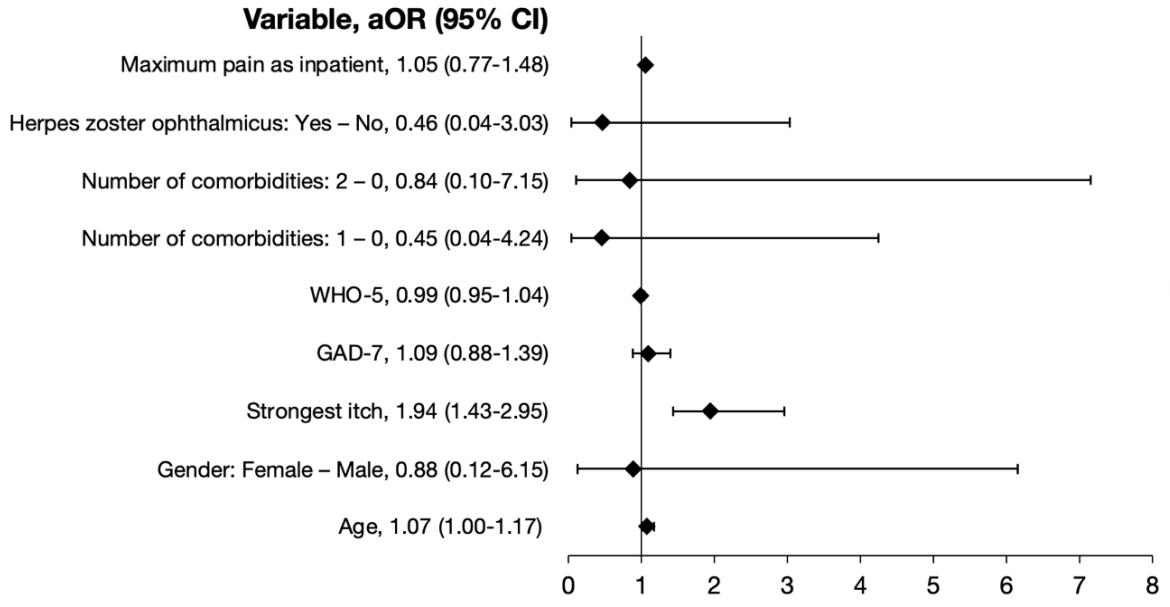
Abbreviations/Acronyms: CI (confidence interval), CIUS (Compulsive Internet Use Scale), GAD-7 (Generalized Anxiety Disorder 7), inf (infinity), OR (odds ratio), WHO-5 (WHO-Five Well-Being Index)

Figure 11: Forest plot of the univariable binomial logistic regression analyses of all analyzed variables in relationship to the risk of developing postherpetic neuralgia. The black diamond represents the odds ratio (OR), and the error bars indicate a 95% confidence interval (CI)

Table 9: Results of univariable binomial logistic regressions of the association between postherpetic neuralgia and age, gender, itch severity in the last 24 hours, anxiety (GAD-7), depression (WHO-5), cigarette smoking, alcohol consumption, HZO, inpatient antiviral treatment duration, and maximum pain severity during inpatient treatment

Variable	Univariable		
	OR	**95% CI**	***p* value**
Age	1.08	1.03-1.14	.002
Gender (Reference: Male)			
Female-Male	1.19	0.42-3.44	.742
Average itch	2.44	1.61-3.70	<.001
Strongest itch	2.11	1.53-2.91	<.001
GAD-7	1.09	0.97-1.22	.146
WHO-5	0.98	0.96-1.00	.120
Cigarette smoking (Reference: Nonsmoker)			
Former smoker – Nonsmoker	0.53	0.14-2.08	.362
Non-daily smoker – Nonsmoker	2.59E-08	0.00-inf	.995
Daily smoker – Nonsmoker	2.59E-08	0.00-inf	.993
Alcohol risk (Reference: Lower risk)			
Higher risk – Lower risk	1.79	0.49-6.51	.376
Binge drinker (Reference: No)			
Yes – No	1.53	0.28-8.35	.621
Number of comorbidities (Reference: 0)			
1 – 0	1.08	0.28-4.15	.914
2 – 0	1.87	0.52-6.71	.339
Herpes zoster ophthalmicus (Reference: No)			
Yes – No	1.29	0.45-3.69	.641
Acyclovir therapy duration	1.34	0.92-1.97	.131
Maximum pain as inpatient	1.1	0.90-1.35	.345

Abbreviations/Acronyms: aOR (adjusted odds ratio), CI (confidence interval), GAD-7 (Generalized Anxiety Disorder 7), HZO (herpes zoster ophthalmicus) inf (infinity), OR (odds ratio), WHO-5 (WHO-Five Well-Being Index)



Abbreviations/Acronyms: aOR (adjusted odds ratio), CI (confidence interval), GAD-7 (Generalized Anxiety Disorder 7), inf (infinity), OR (odds ratio), WHO-5 (WHO-Five Well-Being Index)

Figure 12: Forest plot of the multivariable Firth logistic regression analysis of all variables of interest (age, gender, strongest itch scores, anxiety as GAD-7 scores, mental well-being as WHO-5 scores, ophthalmic nerve involvement, the number of comorbidities, and the maximum pain reported during inpatient treatment) in relationship to the risk of developing postherpetic neuralgia. The black diamond represents the adjusted odds ratio (aOR), and the error bars indicate a 95% confidence interval (CI)

Table 10: Results of a multivariable Firth logistic regression of the association between postherpetic neuralgia and age, gender, strongest itch severity in the last 24 hours, anxiety (GAD-7), depression (WHO-5), herpes zoster ophthalmicus, inpatient antiviral treatment duration, and maximum pain severity during inpatient treatment

Variable	Multivariable		
	OR	**95% CI**	***p* value**
Age	1.07	1.00-1.17	.040
Gender (Reference: Male)			
Female-Male	0.88	0.12-6.15	.891
Strongest itch	1.94	1.43-2.95	<.001
GAD-7	1.09	0.88-1.39	.412
WHO-5	0.99	0.95-1.04	.709
Number of comorbidities (Reference: 0)			
1 – 0	0.45	0.04-4.24	.474
2 – 0	0.84	0.10-7.15	.862
Herpes zoster ophthalmicus (Reference: No)			
Yes – No	0.46	0.04-3.03	.422
Acyclovir therapy duration			
Maximum pain as inpatient	1.05	0.77-1.48	.742

Abbreviations/Acronyms: aOR (adjusted odds ratio), CI (confidence interval), GAD-7 (Generalized Anxiety Disorder 7), HZO (herpes zoster ophthalmicus) inf (infinity), OR (odds ratio), WHO-5 (WHO-Five Well-Being Index)

4. Internet search data

4.1. Materials and methods

4.1.1. Study design

Google Ads Keyword Planner was used to evaluate the web search volume for keywords related to HZ from October 2016 to September 2020 (Kain et al., 2023). Originally developed for marketing purposes, the software has recently seen applications in scientific investigations (Zink et al., 2019). Google Ads Keyword Planner provides a list of relevant search terms and their search volume for the last 48 months after entering a particular word or phrase, which in this study were “herpes zoster” and the German layman’s term for shingles (“Gürtelrose”). Data were collected for Germany as a whole and its 16 federal states. Only data for searches made in Germany and with German set as the preferred language were considered. As data for the study used publicly available search terms, institutional review board approval was not required, and informed consent was not applicable.

4.1.2. Classification

All identified keywords were qualitatively assessed and classified as either relevant or irrelevant keywords (Kain et al., 2023). Search terms that did not mention HZ, were inapplicable because they, for example, related to only animals, or were repetitions of the same keywords were excluded from further analyses. The remaining relevant search terms were classified into 11 categories that are summarized in Table 11.

Table 11: Eleven categories formed for the classification of herpes zoster-related keywords used in web searches in Germany from October 2016 to September 2020

Category	Example keyword	Translation
General	gürtelrose	shingles
Localization	gürtelrose gesicht	shingles face
Symptoms and severity	gürtelrose symptome	shingles symptoms
Contagiousness	ist gürtelrose ansteckend	is shingles contagious
Therapy	gürtelrose behandlung	shingles treatment
Causes	windpocken gürtelrose	chickenpox shingles
Patient characteristics	gürtelrose kind	shingles child
Complications	postherpetische neuralgie	postherpetic neuralgia
Information	gürtelrose wikipedia	shingles wikipedia
Vaccine	impfungen gürtelrose	vaccines shingles
Other diseases	gürtelrose hiv	shingles hiv

Where applicable, subcategories for categories were formed for further insight into search behavior. Subcategories were therefore formed for the categories *localization*, *symptoms and severity*, *therapy*, *causes*, *patient characteristics*, and *complications*. As keywords that matched several criteria were assigned to multiple categories and subcategories, cumulative percentages may have exceeded 100%.

To identify seasonal differences in search behavior, the average monthly search volume for spring (March to May), summer (June to August), autumn (September to November), and winter (December to February) in Germany was calculated. Data for the year 2016 were excluded when analyzing search volume over time due to the low number of observations. To assess differences in search volume between the German federal states, the search volume was calculated per 100,000 inhabitants for all federal states and Germany as a whole (Statistisches Bundesamt, 2021).

4.1.3. Statistical analysis

After the assumptions of ANOVA were not met, Welch's ANOVA was conducted to evaluate changes over time and regional differences (Kain et al., 2023). The assumptions were checked with Levene's test for variance homogeneity and Q-Q Plots for normal distribution. Independence was assumed. The Bonferroni test was used for post-hoc analyses. To evaluate the role of regional differences on search interest, Pearson's correlation coefficient was used to analyze the relationship between search volume and population density per km^2 (Statistisches Bundesamt, 2021), the number of inhabitants per working physician for each federal state (Bundesärztekammer, 2021), and the number of dermatologist per 100,000 inhabitants registered in each federal state (Kassenärztliche Bundesvereinigung, 2021). The significance level was set to .05. For all statistical analysis, the open-source software JASP version 0.16.1 was used (University of Amsterdam, Netherlands) (JASP Team, 2022).

4.2. Results

4.2.1. Overview

For Germany, 1,694 keywords related to HZ were identified, of which 43 were considered irrelevant and were excluded from analyses (Kain et al., 2023). Fifteen examples for keywords excluded from analysis are listed in Table 12. The remaining 1,651 keywords had a total search volume of 20,816,210 searches, translating to 25,033 searches per 100,000

inhabitants. The keyword with the highest search volume was the German layman's term for shingles ("Gürtelrose") followed by "shingles contagious" ("Gürtelrose ansteckend") and "shingles symptoms" ("Gürtelrose symptome") (Table 13).

Table 12: Fifteen examples for keywords including their English translations excluded from web search data analyses of herpes zoster-related keywords in Germany from October 2016 to September 2020

Keyword	Translation
abgeheilte windpocken	healed chickenpox
gibt es gürtelrose beim hund	is there shingles in dogs
gürtelrose ansteckend für hunde	shingles contagious for dogs
gürtelrose ansteckend für pferde	shingles contagious for horses
gürtelrose ansteckend hund	shingles contagious dog
gürtelrose auf tiere übertragbar	shingles transmissable to animals
gürtelrose hund	shingles dog
gürtelrose katze	shingles cat
sind windpocken ansteckend wenn man sie schon hatte	are chickenpox contagious when you already had them
windpocken 2x bekommen	get chickenpox 2x
windpocken ansteckend erwachsene	chickenpox contagious adults
windpocken ansteckung durch dritte	chickenpox contagious adults from third party
windpocken mehrfach bekommen	get chickenpox multiple times
windpocken schmerzen	chickenpox pain
windpocken wieder bekommen	get chickenpox again

Table 13: Ranking of the twenty herpes zoster-related keywords with the highest total search volume in Germany from October 2016 to September 2020 including their English translations as well as their corresponding keyword categories

Rank	Keyword	Translation	Category	Search volume
1	gürtelrose	shingles	General	10,508,000
2	gürtelrose ansteckend	shingles contagious	Contagiousness	1,131,600
3	gürtelrose symptome	shingles symptoms	Symptoms	546,400
4	gesichtsrose	facial shingles	Localization	504,900
5	gürtelrose im gesicht	shingles in face	Localization	325,200
6	gürtelrose behandlung	shingles therapy	Therapy	276,600
7	gürtelrose dauer	shingles duration	General	223,300
8	ist gürtelrose ansteckend	is shingles contagious	Contagiousness	216,200
9	gürtelrose gesicht	shingles face	Localization	207,700

10	zoster	zoster	General	204,600
11	gürtelrose krankschreiben	shingles sick leave	Information	143,530
12	impfungen gürtelrose	vaccines shingles	Vaccine	143,290
13	symptome gürtelrose	symptoms shingles	Symptoms	117,800
14	gürtelrose ursachen	shingles causes	Causes	108,500
15	gürtelrose schmerzen	shingles pain	Symptoms	94,720
16	varizella zoster	varicella zoster	Causes	90,700
17	gürtelrose frühstadium	shingles early stage	General	90,070
18	gürtelrose am kopf	shingles on the head	Localization	87,600
19	post zoster neuralgie	postherpetic neuralgia	Complications	79,800
20	gürtelrose rücken	shingles back	Localization	77,130

4.2.2. Search volume over time

The average search volume per month per 100,000 inhabitants increased during the study period (Figure 13). Differences between the years were found ($p < .001$). In 2017, an average of 400.7 (± SD 20.7) searches per month per 100,000 inhabitants were conducted. This increased to 445.8 (± SD 44.7, p = .0644) searches per month in 2018, to 604.0 (± SD 103.9, $p < .001$) in 2019, and to 724.0 (± SD 69.6, $p < .001$) in 2020. The average search volume in 2020 was higher than in 2019 ($p = .001$). The lowest search volume was observed for December 2016 and the highest for August 2020 (Figure 13).

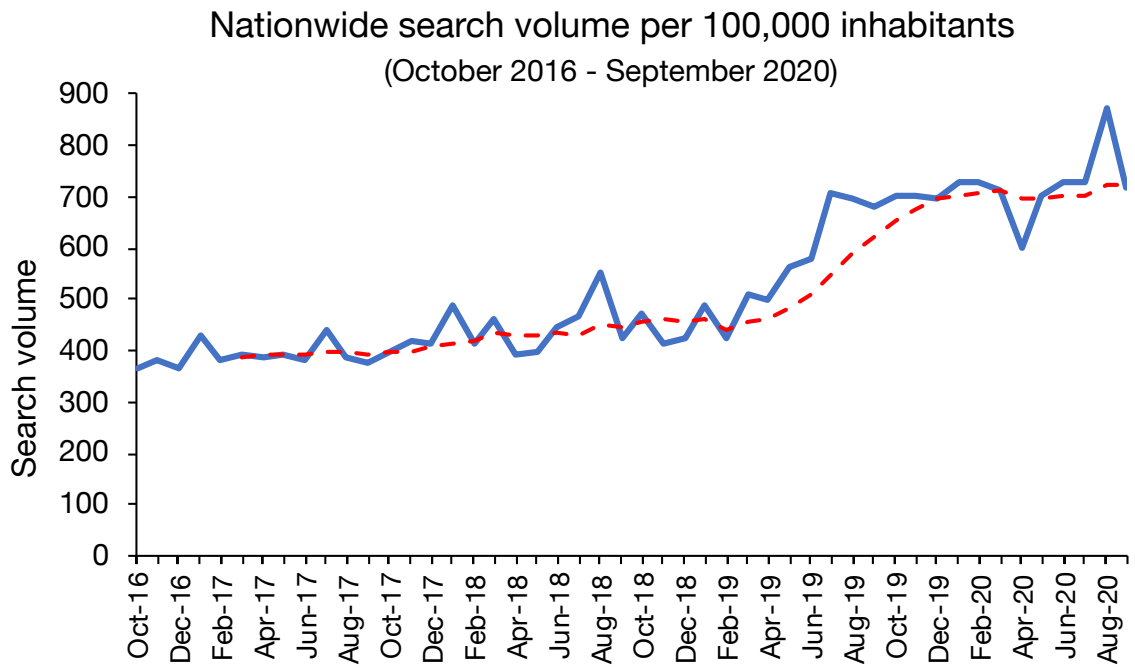


Figure 13: Nationwide search volume for herpes zoster-related web searches in Germany from October 2016 to September 2020. The moving average trendline is represented by the dashed red line

However, no differences in search volume by season were found (spring: 500.9 ± SD 119.9; summer: 581.2 ± SD 161.7; autumn: 504.7 ± SD 147.0; winter: 499.3 ± SD 137.1; p = .53) (Figure 14).

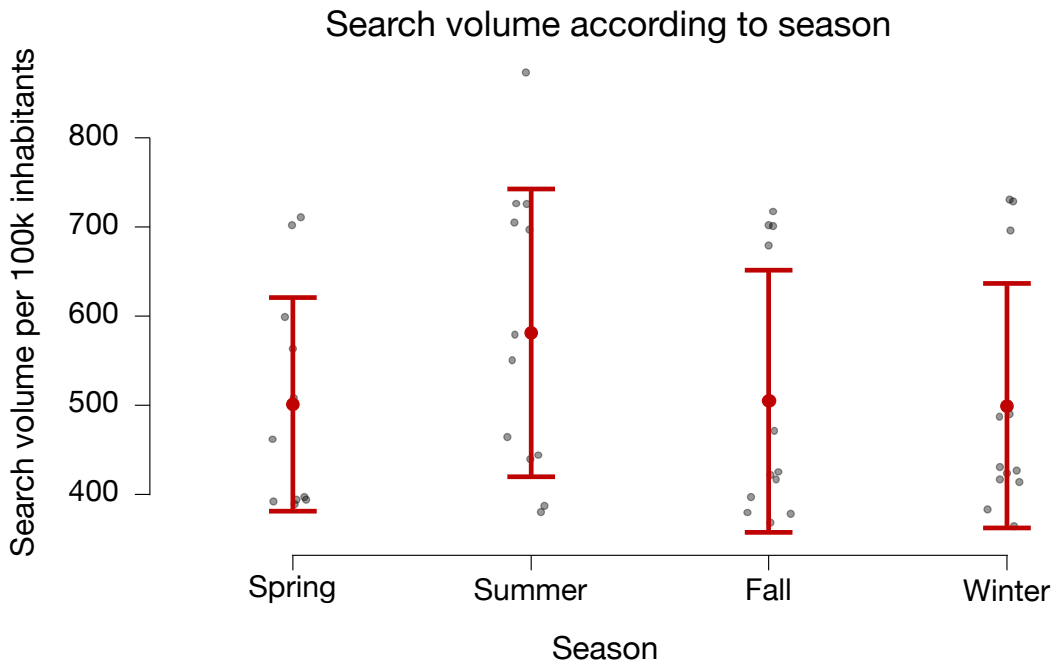


Figure 14: Jitter plot of the herpes zoster-related web search volume in Germany per 100,000 inhabitants for the four seasons. Springtime included the months of March to May, summer the months of June to August, autumn the months of September to November, and winter the months of December to February. The red center dot represents the mean value, with red errors bars representing the standard deviation

4.2.3. Keyword categories

The category with the highest overall search volume was the category *general*, with 11,475,560 (55.1%) searches, followed by the categories *localization* and *symptoms and severity*, with 3,567,790 (17.1%) and 2,130,210 searches (10.2%), respectively (Table 14). Searches related to *other diseases* and a shingles *vaccine* had the lowest search volumes, with 0.4% and 0.8% of the total search volume, respectively.

Table 14: Keyword categories, their search volume, and their percentage* of the total search volume for the web search volume of herpes zoster-related keywords in Germany

Category	Number of keywords	Search volume	Percentage of total search volume*
General	132	11,476,110	55.1%
Localization	558	3,567,790	17.1%
Symptoms and severity	334	2,130,210	10.2%
Contagiousness	136	1,837,870	8.8%
Therapy	198	855,570	4.1%
Causes	128	518,330	2.5%
Patient characteristics	137	510,470	2.5%
Complications	139	465,090	2.2%
Information	122	395,870	1.9%
Vaccine	19	163,740	0.8%
Other diseases	66	76,630	0.4%

* As keywords were assigned to multiple categories if they met several criteria, the sum of keywords for each category and the sum of the search volume for each category exceed the total number of keywords (n = 1,651) and overall search volume (n = 20,816,210), respectively. The percentages of the total search volume were calculated by dividing the search volume per category by the total search volume. The total percentage therefore exceed 100%.

In the *localization* category, most searches related to the face (39.6%), followed by the legs (8.9%) and head in general (8.8%) (Figure 15). In the category *symptoms and severity*, 41.2% of searches were general queries, with searches about pain (17.1%) and skin changes (13.2%) being the two most searched for specific symptoms (Table 15). After general searches, searches for alternative therapy (20.4%) had the highest search volume in the category therapy. In the *causes* category, nearly half of searches related to chickenpox or varicella (46.2%) followed by general queries (38.2%). Regarding *patient characteristics*, most searches were about children (52.9%) and pregnant individuals (34.2%). Searches about PHN constituted the majority of searches in the *complications* category (59.8%).

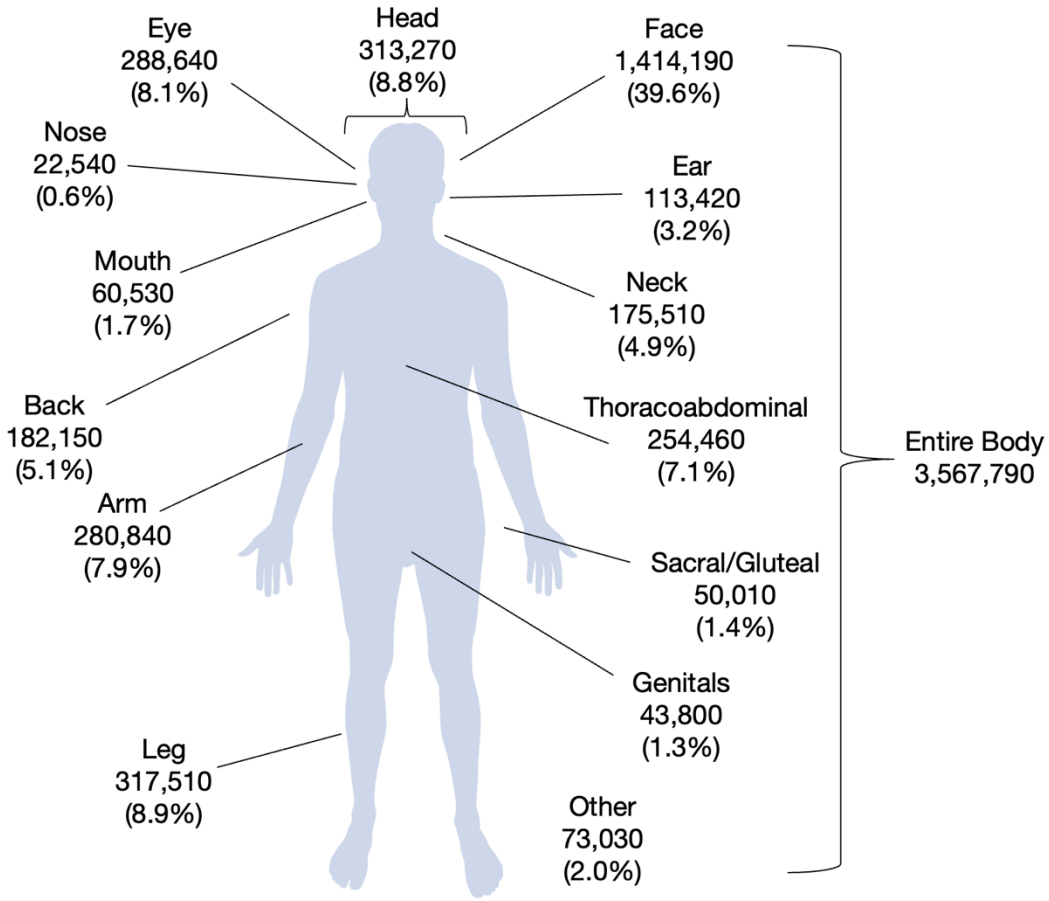


Figure 15: Search volume of herpes zoster-related web searches in Germany from October 2016 to September 2020 grouped according to body localizations

Table 15: Internet search volume for select categories and their five largest subcategories with respective percentages for herpes zoster-related keywords in Germany.

Category	Search volume	Top 5 subcategories (by search volume)*				
Localization	3,567,790	Face *n* = 1,414,190 (39.6%)	Leg *n* = 317,510 (8.9%)	Head *n* = 313,270 (8.8%)	Eye *n* = 288,640 (8.1%)	Arm *n* = 280,840 (7.9%)
Symptoms and severity	2,130,210	General *n* = 877,130 (41.2%)	Pain *n* = 364,110 (17.1%)	Skin/Blisters *n* = 280,150 (13.2%)	Absence *n* = 238,870 (11.2%)	Other *n* = 41,500 (1.9%)
Therapy	855,570	General *n* = 560,120 (65.5%)	Alternative *n* = 174,750 (20.4%)	Medication *n* = 68,580 (8.0%)	No therapy *n* = 17,880 (2.1%)	Physician *n* = 17,550 (2.1%)
Causes	518,330	Chicken-pox/Patho-gen *n* = 239,670 (46.2%)	General *n* = 185,450 (35.8%)	Stress *n* = 33,310 (6.4%)	Mental/Spir-itual *n* = 30,930 (6.0%)	Other *n* = 14,730 (2.8%)
Patient char-acteristics	510,470	Children *n* = 269,830 (52.9%)	Pregnancy *n* = 174,550 (34.2%)	Adults *n* = 26,120 (5.1%)	Elderly *n* = 23,760 (4.7%)	Young peo-ple *n* = 9,580 (1.9%)
Complications	465,090	PHN *n* = 278,030 (59.8%)	General *n* = 100,610 (21.6%)	Death *n* = 49,530 (10.6%)	Other *n* = 25,640 (5.5%)	Scarring *n* = 11,280 (2.4%)

Abbreviations/Acronyms: PHN (postherpetic neuralgia)

* As keywords were assigned to multiple subcategories if they met several criteria, the sum of keywords and the sum of the search volume for each subcategory may exceed the total number of keywords and search volume for each category, respectively. Percentages for the subcategories were calculated by dividing the search volume per subcategory by the category search volume. The total percentages therefore may exceed 100%.

4.2.4. Comparison between the German federal states

For Germany, the average search volume per month was 521.5 (± SD 141.2) searches per 100,000 inhabitants. Among the federal states, the highest monthly search volume per 100,000 inhabitants was observed for Hamburg (963.5 ± SD 211.7) followed by Saarland (855.7 ± SD 188.7) and Bremen (850.1 ± SD 147.0) (Table 16). The search volume for these three states was significantly higher than the observed lowest monthly search volume per 100,000 inhabitants in Baden-Württemberg (541.9 ± SD 138.3), followed by that in Bavaria (546.9 ± SD 144.1) and North Rhine-Westphalia (581.2 ± SD 152.8) (Table 16).

Table 16: Average monthly herpes zoster-related Google search volume per 100,000 inhabitants for Germany as a whole and its sixteen federal states from October 2016 to September 2020 in decreasing order

State	Average monthly search volume per 100,000 inhabitants	Standard deviation
Hamburg	963.5	211.7
Saarland	855.7	188.7
Bremen	850.1	147.0
Berlin	728.4	136.7
Mecklenburg-Western Pomerania	725.2	175.4
Thuringia	683.3	146.4
Saxony-Anhalt	679.0	157.4
Schleswig-Holstein	666.2	169.6
Saxony	655.3	155.4
Brandenburg	647.1	164.0
Hesse	635.7	143.3
Rhineland-Palatinate	627.0	145.2
Lower Saxony	585.2	141.6
North Rhine-Westphalia	581.2	152.8
Bavaria	546.9	144.1
Baden-Württemberg	541.9	138.3
Germany	521.5	142

High positive correlations were demonstrated between the average monthly search volume per 100,000 inhabitants and population density (r = .51 p = .043) and number of dermatologists per 100,000 inhabitants (r = .69, p = .003) (Figure 16). Inversely, there was a strong negative correlation between the average monthly search volume and the number of inhabitants per working physician in each federal state (r = -.69, p = .003) (Figure 17).

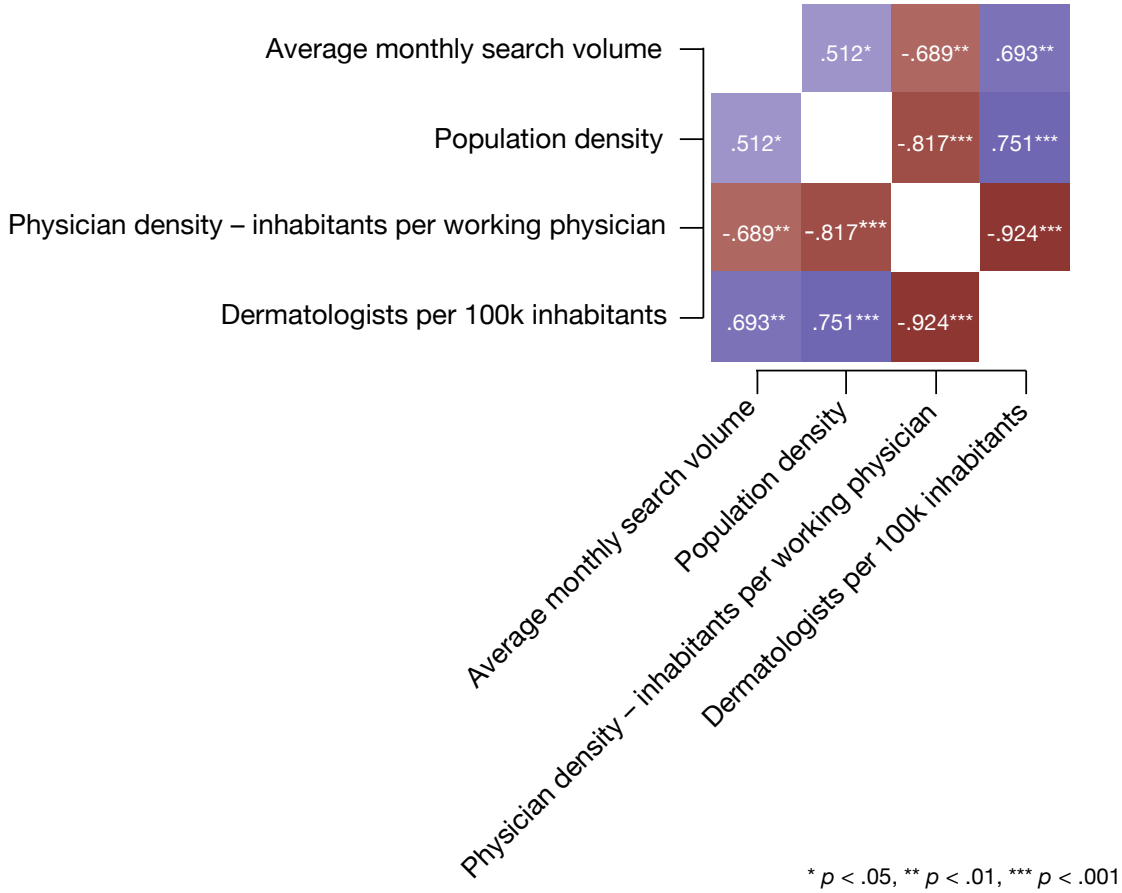


Figure 16: Heatmap for Pearson's correlation coefficients for the relationship between average monthly web search volume per 100,000 inhabitants of herpes zoster-related keywords, population density, physician density expressed as the number of inhabitants per working physician, and the number of registered dermatologists per 100,000 inhabitants for the federal states in Germany. Increasingly darker purple color indicates positive correlations, and increasingly darker red color indicates negative correlations

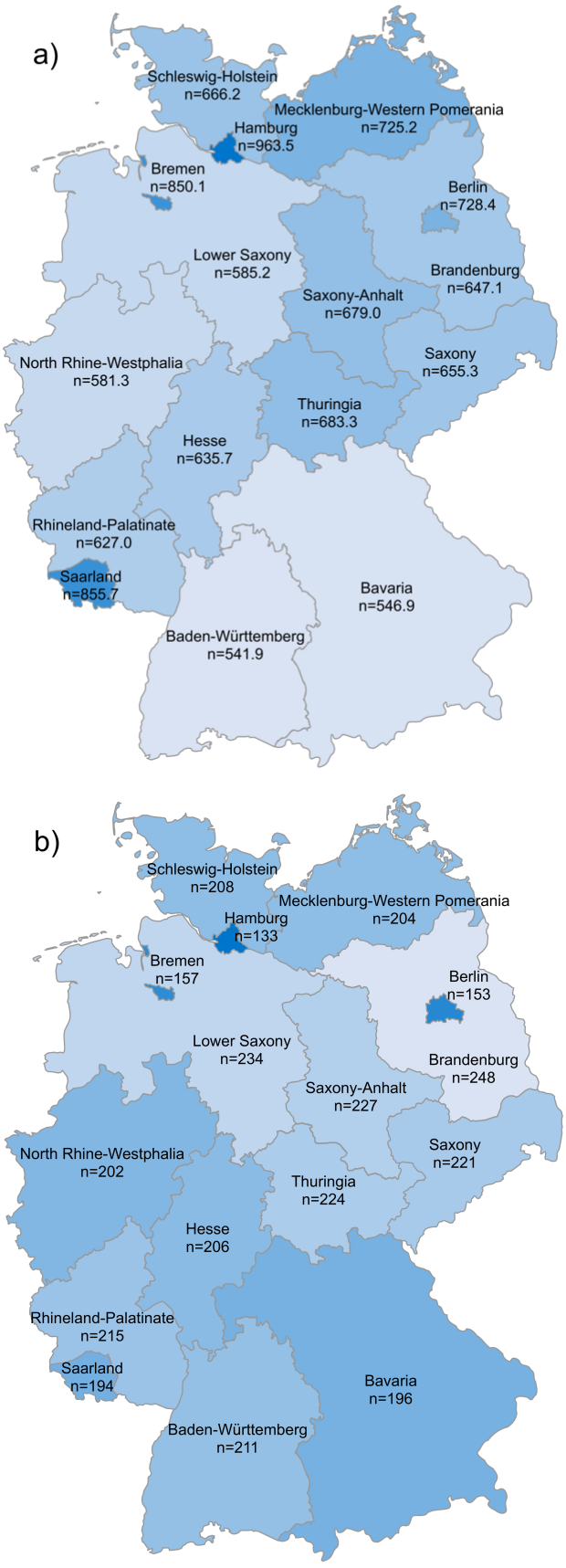


Figure 17: a) Average monthly search volume per 100,000 inhabitants for herpes zoster-related keywords for the sixteen German federal states and b) the physician density in each German federal state expressed as the number of inhabitants per working physician

5. Discussion

5.1. Questionnaire and patient medical records study

Using questionnaire and medical records data from participants recruited in a traditional clinical setting, this part of the study aimed to evaluate the disease burden of PHN and identify associated factors for PHN. Overall, participants suffering from PHN were older than participants who were not. Participants with PHN not only reported higher interference of daily activities because of their pain, but also were more likely to have anxiety and worse mental well-being scores. Furthermore, a higher number of comorbidities and greater itch severity were observed for participants with PHN. The results of this study underline the high disease burden associated with PHN, which also encompasses the negative impact of the disease on mental health.

5.1.1. Prevalence and age

The prevalence of PHN in this study was 18.5% for the complete cases used for regression analysis and 26.0% for the entire study population. Gauthier et al. reported an overall prevalence of PHN of 13.7% or 19.5% depending on the definition used for PHN (2009). However, as several studies have demonstrated, the risk of developing PHN is age dependent. For example, Kost and Straus found in the literature a PHN prevalence of 27%, 47%, and 73% for untreated adults older than 55, 60, and 70 years, respectively (1996). An American study analyzed medical records data from approximately 900 patients and reported a prevalence of 18% in patients older than 50 years and 37% in patients older than 60 for PHN with a pain duration of more than a year (de Moragas & Kierland, 1957). The prevalence rates calculated in our study fall within the ranges reported in the literature and showed similar variations according to age.

5.1.2. Factors associated with PHN

As the varying prevalence rates illustrate, age is one of the primary risk factors for PHN. In addition to participants in the study with PHN being older, univariable and multivariable logistic regressions showed a significant association between age and PHN. Age is one of the most well-known risk factors for PHN, and the relationship between age and PHN has been demonstrated by multiple studies (Forbes et al., 2016b; Gauthier et al., 2009; Helgason et al., 2000; Hope-Simpson, 1975).

Unlike age, the role of gender as a risk factor in PHN is less well understood (Amicizia et al., 2017). Some studies have demonstrated that women are not only more likely to develop HZ (Fleming et al., 2004; Ultsch et al., 2011), but are also at a higher risk for developing PHN (Gauthier et al., 2009; Hope-Simpson, 1975; Jung et al., 2004; Parruti et al., 2010). In contrast, Bouhaissira et al. observed that male gender was a predictive factor for PHN (2012). Amicizia et al. analyzed the relationship between age and gender and found that older men were more likely to develop PHN than younger men, with no relationship between age and gender being observed for women (2017). In contrast, our study reported no substantial relationship between gender and PHN, which is line with findings from numerous other studies (Choo et al., 1997; Opstelten et al., 2002; Wei et al., 2019). The lack of consensus about the role of gender on PHN may reflect differences in study methodology, as Forbes et al. observed in a meta-analysis that the influence of gender varied depending on the age of the study population (2016b).

Some studies have reported on a relationship between disease localization and the risk of developing PHN, which may be also related to risks associated with increasing age. For example, HZ with an ophthalmic localization was identified as a predictive factor for the development of PHN (Coen et al., 2006; Opstelten et al., 2002). In another study, HZ patients with trigeminal involvement were more likely to have PHN of longer duration (de Moragas & Kierland, 1957). Patients with PHN were more likely to have had HZO than HZ affecting other localizations when compared with HZ patients without PHN (Volpi et al., 2008). Trigeminal (Brown, 1976) and ophthalmic (Borkar et al., 2013; Ragozzino et al., 1982) HZ localizations have been associated with older age. In contrast, other studies have reported no notable influence of age on the development of HZO (Ghaznawi et al., 2011). In our study, ophthalmic involvement did not appear to be associated with the presence of PHN. Discrepancies in study outcomes may be due to different participant recruitment methods, with participants in this study only being recruited from a university clinic and other studies analyzing EMRs data from larger databases (Opstelten et al., 2002) or recruiting via GP offices (Coen et al., 2006). This can be observed in the overrepresentation of patients with HZO in the inpatient study population, as patients with HZO tend to have worse clinical outcomes that may warrant inpatient treatment (Galil et al., 1997).

However, Hope-Simpson also noted that HZ localization did not influence the PHN incidence itself and that cranial involvement was only associated with a longer PHN duration (Hope-Simpson, 1975), which was an aspect of PHN measured for a subset of the study population in the present study. Most participants with PHN symptoms at the time of study participation

who were treated inpatient for HZ had a disease duration of at least one year, with the mean disease duration exceeding two years. In the literature, various ranges for the PHN disease duration have been reported. Gauthier et al. reported a mean disease duration of 7.5 or 9 months depending on which definition of PHN was considered (2009), which was notably shorter than the mean disease duration calculated in this study. Other studies have reported on longer disease durations for PHN. For example, Oster et al. reported a range of 3 months to more than 10 years for PHN disease duration in a study that calculated a mean of 3.3 years (2005). Disease durations of more than five years were also reported by Helgason et al., although most participants did not continue experiencing pain after twelve months (2000). As with other aspects related to HZ and PHN, age may influence the PHN disease duration. Nearly half (47.5%) of participants aged 70 years and older had experienced chronic pain more than a year after their initial HZ infection compared with only 4.2% of participants younger than 20 years old in a study by de Moragas and Kierland (1957). While the present study did not analyze the relationship between age and PHN disease duration, the overall older age of the study population may have played a role in the long disease duration observed here. However, it is important to consider that differences in study methodology and data reporting may be responsible or variations in disease duration found in the literature (Johnson et al., 2010). Moreover, the definition for disease duration employed in this study limits possibilities for comparison, as only individuals with PHN symptoms at the time of study participation were considered and participants with significantly shorter disease durations were not identified as having PHN. Future studies should use a prospective study design to better document the PHN disease duration.

Another HZ disease characteristic identified in the literature as a risk factor for PHN is high acute pain severity during the initial HZ infection (Drolet et al., 2010a; Jung et al., 2004; Parruti et al., 2010). A study from Italy showed that HZ patients with PHN reported higher median pain scores than those without PHN (Volpi et al., 2008). This association between acute pain severity, which was measured as the maximum reported pain level during inpatient treatment, and PHN was not observed in our study. As with the PHN disease duration, this may be due to the retrospective nature of the study, as prospective studies are more likely to accurately assess the acute pain of HZ patients by explicitly asking participants about their pain related to HZ and documenting changes in pain through the entire disease course. While we assume that participants were accurately asked to rate their HZ-related pain during their inpatient stay, there are no possibilities to confirm what and how they were asked by the medical staff. The benefits of a prospective study design can be observed in a study by Drolet et al., who

calculated the area under the curve for the worst reported shingles-related pain from the ZBPI over a period of 180 days to create a HZ Severity-of-Illness score, which demonstrated to be a predictive score for PHN (2010a).

As Gauthier et al. reported, patients who develop PHN tend to have overall poorer health than those who do not, with a higher proportions of patients with PHN having certain disease comorbidities (2009). In our study, one aspect of participant health that was examined was the total number of comorbidities. In regression analyses, the number of comorbidities was not shown to be a significantly associated variable for PHN. However, the regression analyses were only conducted on a subset of participants who were treated inpatient for HZ, who may overall for several reasons be in a poorer state of health that would warrant inpatient treatment in the first place, thereby masking the influence of the number of comorbidities. In the more representative sample of the entire study population, comprising patients treated in- and outpatient for HZ, the number of comorbidities did show significant differences in chi-square tests and supported findings from other studies that identified disease comorbidities as a risk factor for PHN. For example, patients suffering from HZ complications were more likely to have disease comorbidities like cancer, diabetes, and inflammatory bowel disease (Galil et al., 1997). In another study, researchers found asthma, autoimmune diseases, and chronic kidney diseases to be some of the comorbidities associated with PHN (Forbes et al., 2016a).

Health was also evaluated in this study through addictions and lifestyle factors like cigarette smoking and alcohol consumption habits. While some studies have demonstrated an association between internet addiction and chronic inflammatory skin diseases like psoriasis (Schielein et al., 2021; Schielein et al., 2020), no such relationship was observed for PHN in this study. HZ and PHN primarily affecting older individuals may be a reason for this observation (Kost & Straus, 1996). Studies on internet addiction have shown that moderate to severe internet addiction is less likely to affect older adults (Devine et al., 2022). Similarly, no association was observed between PHN and alcohol consumption as either alcohol risk level or binge drinking habits in this study. Although this is a subject not frequently examined in the literature, no association between alcohol abuse and PHN was seen in the few studies that analyzed alcohol abuse as risk factor for the disease (Forbes et al., 2016b; Parruti et al., 2010). Forbes et al. found that being either a current or former smoker was a risk factor for PHN (2016a), which was also demonstrated in a prospective study from Italy (Parruti et al., 2010). However, another study analyzing group differences between patients with and without PHN found no differences in smoking habits between the two groups (Seetan et al., 2021), which parallels the findings of our study. In one study from Japan, smoking and drinking habits were

not evaluated for their direct influence on PHN but rather indirectly for their influence on mental health (Takao et al., 2017), which may be the more relevant aspect of disease burden of PHN to assess.

It is important to consider mental health comorbidities when discussing PHN, especially since a relationship between chronic pain and diseases like anxiety (Asmundson & Katz, 2009) and depression (Fishbain et al., 1997) has been well established in the literature. One study has demonstrated that the prevalence of depression and anxiety in patients with PHN exceeded that of patients with other forms of chronic pain like diabetic neuropathy and chronic lower back pain (Du et al., 2021). Additionally, depression has been identified as a risk factor for both HZ (Marin et al., 2016; Schmader et al., 1998) and PHN (Forbes et al., 2016a). Dworkin et al. found that HZ patients who developed PHN showed higher levels of depression and anxiety than patients who did not develop PHN (1992). Johnson argues that these findings suggest that the pathogenesis of PHN includes the involvement of psychosocial factors (1995). In the analyses of group differences with the total study population, differences were observed in WHO-5 scores and GAD-7 scores for participants with and without PHN. For the WHO-5, participants with PHN reported scores indicating worse mental well-being. For the GAD-7, participants with PHN reported a median score indicative of mild anxiety compared to a median score indicating no anxiety for participants without PHN. However, no notable association was observed in the logistic regressions using the inpatient study population. As with the number of comorbidities, this difference in outcome may be attributed to the different study populations for each analysis, with the overall study population providing a more representative sample of individuals who are affected by HZ and therefore more accurately reflecting the relationship between mental health and PHN. Furthermore, the retrospective nature of the study can only identify a relationship between mental health and PHN and not elucidate on whether poor mental health outcomes are a cause for or a result of PHN. Nevertheless, as the literature shows, mental health comorbidities are likely to be both (Du et al., 2021; Forbes et al., 2016a; Gerrits et al., 2014; Takao et al., 2017).

5.1.3. Impact on QoL

As the differences in the ZBPI pain interference scores illustrate for patients with and without PHN in this study, PHN negatively impacts activities of daily life. This negative influence of PHN on QoL has been previously shown in the literature, with particularly mood, sleep, and enjoyment of life being impaired (Drolet et al., 2010b). Several studies have demonstrated a positive correlation between PHN pain severity and HRQoL (Drolet et al., 2010b; Oster et al., 2005; van Seventer et al., 2006), which was similarly shown in this study, as correlations were

observed between worst pain severity and interference of daily activities, GAD-7 scores, and WHO-5 scores. Inversely, being limited in conducting daily activities was identified as a risk factor for PHN (Drolet et al., 2010a). Drolet et al. also noted that age is a significant factor that influences QoL in patients with PHN (2010b) and as seen in this study, pain severity. With older adults being more likely to develop PHN despite receiving recommended treatment (Bouhassira et al., 2012), these results underscore the importance of HZ and thereby PHN prevention in minimizing the negative impact of PHN on QoL.

The results from the present study indicate that chronic pain may not be the only factor that influences HRQoL and mental well-being of patients suffering from PHN. Results of the Mann-Whitney U tests and logistic regression analyses showed that itch was a symptom strongly associated with PHN. Itch is a common symptom of acute HZ infection, but it can also manifest itself as a complication of HZ as postherpetic itch (PHI) (Oaklander, 2017). PHI is defined as a neuropathic itch caused by nerve inflammation and damage (Ishikawa et al., 2018). Little research (Oaklander et al., 2003) and few clinical trials (Oaklander, 2017) have been conducted for PHI, and little is known about its exact etiology (Ishikawa et al., 2018) despite it not being a rare complication of HZ (Oaklander et al., 2003).

PHI is capable of causing significant physical damage and disability, with one case report documenting a patient suffering from frontal skull and brain damage caused by scratching (Oaklander et al., 2002). Chronic itch in general has been associated with a negative impact on QoL similar to that of chronic pain (Kini et al., 2011) as well as clinical depression and suicidal ideation (Dalgard et al., 2020). However, PHI in particular was shown to have no impact on QoL in a Dutch study with over 600 participants (van Wijck & Aerssens, 2017). As PHI was not the primary outcome investigated in this study, no conclusions can be made about the definitive impact of PHI on QoL. Additionally, as PHI can exist without PHN (Ishikawa et al., 2018), individuals who only experience itching were not included in the study, so that current results may underestimate any impact from chronic itch. Since PHI is often not sufficiently addressed by treatments used for PHN (Ishikawa et al., 2018), PHI may represent an important contributor to the HZ disease burden and warrants further investigation. Considering the lack of studies on PHI, future research should evaluate the impact of PHI independent of PHN.

5.1.4. Limitations

Several study limitations require further discussion. First, while diagnostic codes were used to identify patients with HZ eligible for study inclusion, they were not used to identify

participants with PHN. Instead, only participant reported pain levels were used to identify those affected by PHN. This method is subject to participant reporting errors and may have resulted in incorrect classifications of participants with and without PHN. Additionally, the retrospective nature of the study meant that participants who previously had symptoms indicative PHN but who no longer had these symptoms at the time of study participation were not classified as having the disease. In other words, a participant may have had chronic pain shortly after his or her HZ disease in the year 2017, which was resolved by the time he or she filled out the questionnaire in 2020. The standardized ZBPI questionnaire only inquired about pain occurring in the last 24 hours for the PHN classification. This recruitment methodology may have resulted in an underestimation of the risk of PHN as well as overestimation of the disease duration, as patients who previously had PHN of a shorter duration were not considered as having PHN at all. Disease duration was only measured for those patients who were still experiencing symptoms at the time of study participation, which would only include participants who had PHN of a longer duration considering the timeframes for recruitment and data collection. Nevertheless, the prevalence rates and the observed disease duration for PHN in this study fell within the ranges reported in the literature. Future prospective studies may improve and complement the findings reported in the present study.

As Gauthier et al. explained in their study, where data are collected influences how representative a study population is (2009). Since recruitment only occurred at a university clinic, this may have led to an overrepresentation of patients with more severe forms of disease, patients who are older, or patients who are overall in poorer health, with this overrepresentation being particularly pronounced in regression analyses. Additional recruitment at GP offices likely would have not only expanded the outreach of recruitment but also resulted in a more representative sample of study participants.

As part of the study used questionnaire data, response biases must be considered. For example, participants may have been reluctant to honestly answer questions about alcohol consumption habits and depression as part of a social desirability bias. Non-response bias should also be discussed. During recruitment, several individuals contacted the study team to say that they did not feel the study was relevant to them because they did not experience any complications from HZ. Individuals with PHN were therefore more likely to be motivated to participate in the study than those without PHN. Accordingly, in contrast to the earlier statement about an underestimation of the risk of PHN, a non-response bias may also have resulted in an overestimation of the risk of PHN, as individuals with PHN may be overrepresented in this study population when compared with the general population.

The small sample size for regression analyses is another limitation of the study. As medical records data were only available for participants treated inpatient and only complete cases for the variables were included in regression analyses, substantial data from the entire study population were not considered in these models. For several variables of interest, no significant associations were observed in regression models, which may be attributed to a small sample size as also discussed by Opstelten et al. in their study (2002).

5.2. Internet search data

The aim of this study was to analyze the web search volume for shingles for Germany as a whole and its sixteen federal states, focusing on temporal and geographic factors that modulate search behavior (Kain et al., 2023). Overall, the results demonstrated an increasing interest in HZ in Germany during the 48-month study period, with a total of 20.8 million searches conducted. Comparable studies reported 8.8 million searches for atopic dermatitis (Mick et al., 2021), 11.4 million searches for scabies (Wu et al., 2022), 13.7 million searches for pruritus (Zink et al., 2019), and 19.8 million searches for skin cancer (Seidl et al., 2018) (Table 17). This high search volume for HZ, despite the fact that the disease primarily affects older individuals and that internet use is more common among younger people, underlines the relevance of the internet as a source of health information for HZ (ARD & ZDF, 2022).

Table 17: Overview of select studies analyzing the Google search volume for various health-related topics for Germany with their corresponding total search volume and total number of keywords. Studies are listed in descending order according to total search volume

Reference	Subject	Timeframe	Total search volume	Number of keywords
Kain et al. (2023)	Herpes zoster	October 2016 – September 2020	20,816,210	1,651
Seidl et al. (2018)	Skin cancer	November 2013 – October 2017	19,849,230	646
Tizek et al. (2022)	Atopic dermatitis	January 2017 – December 2020	14,817,610	1,419
Wu et al. (2022)	Scabies	January 2016 – December 2019	11,414,180	572
Wallnöfer et al. (2022)	Psoriasis	September 2016 – August 2020	11,170,740	1,236
Mick et al. (2021)	Atopic dermatitis	January 2016 – December 2019	8,842,360	1,222
Zink et al. (2019)	Pruritus	January 2015 – December 2016	7,531,890	701
Berr et al. (2023)	Axial spondyloarthritis	January 2017 – December 2020	3,881,490	265

Hilker et al. (2021)	Sarcoidosis	July 2015 – June 2019	3,068,200	433
Sitaru et al. (2023)	Allergic asthma	January 2018 – December 2021	1,214,990	321

5.2.1. Search volume over time

Several studies have demonstrated changes in patient behavior in accessing medical care and health information since the COVID-19 pandemic (Guzman & Barbieri, 2020; Searle et al., 2020; Wang et al., 2020). Guzman and Barbieri reported on decreased web search volumes for several dermatological conditions and cosmetic procedures after lockdown announcements in 2020, with only data for general dermatological conditions reaching pre-pandemic levels during the social distancing period (2020). In contrast, another study analyzing web search volume in the United Kingdom during the early phases of the pandemic showed that the search volume for dermatological medical conditions increased during this timeframe. A similar observation was made in the present study for HZ, whose web search volume showed a significant increase from 2019 to 2020 (Kain et al., 2023). This appears to be part of an overall trend of increasing search volume during the study period. Furthermore, studies have reported on an increased risk of developing HZ after a COVID-19 infection, which may be reflected in the increase in search volume during 2020 (Diez-Domingo et al., 2021). Despite the seemingly opposing behaviors in online search interest, our findings may be in line with those of Guzman and Barbieri, who argued that the return to baseline for the search volume of general dermatological conditions may reflect the growing relevance of the internet for health information during a time when access to in-person medical care is limited (Guzman & Barbieri, 2020).

There was no seasonality observed for HZ web search volume (Kain et al., 2023), which has been documented for HZ incidence in some studies (Al-Dahshan et al., 2020; Kim et al., 2014). Al-Dahshan et al. hypothesized that a lack of seasonality in HZ incidence may be attributed to varying immune competency and viral reaction between individuals (2020). In contrast, several studies have reported a seasonality for HZ incidence, with peaks in the summer months (Berlinberg et al., 2020; Gallerani & Manfredini, 2000; Suhail et al., 2016; Toyama et al., 2009). Other studies have also identified the role of UV radiation and higher ambient temperature as risk factors for HZ (Choi et al., 2019; Yang et al., 2015), but the influence of these risk factors on web search data was not demonstrated in this study. As these studies used medical records data, web search data may not be an accurate proxy for disease incidence when analyzing the relationship between HZ and weather. However, Berlinberg et al. were

able to demonstrate seasonality for HZ web search volume, with peaks in the autumn for vaccine-related search volume and peaks in the summer for other HZ-related search terms (2018). Differences in seasonality for web search data may be attributed to geographical and thereby climate differences for the source data as well as differences in statistical analyses between our study and that of Berlinberg et al. (2018).

5.2.2. Keyword categories

After general keywords, most searches related to HZ localizations (Kain et al., 2023). The face, head in general, and eyes were among the five most searched for body localizations. In contrast, more than half of HZ patients have symptoms in thoracic dermatomes, with trigeminal involvement in less than 20% of cases (Han et al., 1994). The greater disease burden for HZ with cranial involvement may explain the increased search volume for these predilection sites. Patients with trigeminal involvement have a higher risk of HZ complications, with HZO increasing the risk sevenfold when compared to the risk associated with thoracic involvement (Galil et al., 1997). PHN, which was the most searched for complication in our study, is the most frequently occurring complication, followed by ocular complications and facial palsies (Volpi, 2007). Similar research on psoriasis web search data has demonstrated that harder-to-treat areas were searched more frequently than typical predilection sites, which may be a pattern also observed for HZ-related search behavior (Wallnöfer et al., 2022).

While HZ can occur in children and young adults, it most commonly affects older adults, with patients 60 years and older comprising half of all cases (Sampathkumar et al., 2009). In contrast, nearly 90% of web searches about patient characteristics related to children or pregnancy (Kain et al., 2023). This suggests a lack of readily available information on typically less-affected demographics like young adults and children. When considering the contagious nature of VZV (Newman & Jhaveri, 2019), queries like “shingles contagious baby” are therefore relevant for both parents and grandparents who may be concerned about possibly infecting at-risk individuals with VZV.

After general therapy inquiries, most searches regarding therapies were for alternative treatment options (Kain et al., 2023). As people often require a prescription for most medication to treat HZ, particularly those individuals with persistent pain (Schmader, 2007), searches for alternative therapies may reflect a lack of access to medical care. Searches for alternative therapy may also indicate dissatisfaction with available treatments. In a French study, 15% of patients with acute HZ and 18% of patients with PHN used complementary medicine to manage their symptoms (Chidiac et al., 2001). A survey on patient satisfaction with HZ

treatments showed that while patients were satisfied with treatment side effects, they were least satisfied with treatment efficacy (Gater et al., 2014). Future studies should investigate the reasons for interest in alternative medicine to treat HZ, particularly to identify possible barriers to medical care and dissatisfaction with treatment options.

5.2.3. Geographic differences

The study demonstrated that regional differences influenced web search behavior, with a high positive correlation observed between population density and average monthly search volume (Kain et al., 2023). Similar geographic variations have been observed for other web search data studies. For example, a positive correlation between population density and web search volume in Germany was observed for scabies-related keywords (Wu et al., 2022). For sarcoidosis, a higher search volume per 100,000 inhabitants was observed in cities compared to the overall national average search volume (Hilker et al., 2021). These differences in search volume may be attributed to demographic differences, with research showing that residents of rural areas in Germany are on average older than those of urban areas and that they use the internet less frequently (Lenz et al., 2005).

However, the accessibility of medical care may also influence search behavior as demonstrated by the correlation between search volume and physician density. Comparable studies using Twitter data have shown that rural areas of the United States discussed the topic of COVID-19 during later stages of the pandemic than more urban areas, showing how place of residence can modulate engagement with the internet for health topics (Cuomo et al., 2020). Cuomo et al. hypothesized that the increase in COVID-19 related Twitter messages in rural communities during later stages of the pandemic may have been a response to a lack of testing services and healthcare access in rural regions (2020). In a study on psoriasis, a positive correlation was observed between the search volume for treatment-related keywords and dermatologist density per 100,000 inhabitants in Germany (Wallnöfer et al., 2022). Rural regions in Germany are more likely to face physician shortages (Ono et al., 2014) and regions with higher physician densities see a higher use of outpatient services (Kopetsch & Schmitz, 2014). In a Canadian study, HZ vaccine dispensing rates were lower for individuals living in rural areas even when adjusting for different access to pharmacies, which researchers believed to be influenced by the low physician density in rural Canada (Liu et al., 2014).

There is conflicting information in the literature on how population density influences HZ incidence and prevalence. Several studies have reported no relationship of HZ incidence along an urban-rural divide (Schmader et al., 1995; Thomas & Hall, 2004). In China, Li et al. reported

on a higher cumulative incidence for HZ in urban areas than in rural areas (2016). A Spanish study on the seroprevalence of anti-VZV antibodies showed higher seroprevalence rates in urban communities than in rural communities (Gil et al., 1998). However, other studies demonstrated higher seroprevalence rates in rural areas, which may the result of larger families being more common in rural communities (de Melker et al., 2006). Moreover, a higher annual incidence and prevalence in rural areas has been observed for HZ in a few European studies (Brănişteanu et al., 2014; Cebrián-Cuenca et al., 2010). While the relationship between place of residence and risk of HZ infection remains unclear, the lack of search interest in less densely populated regions may indicate the need for targeted awareness campaigns for higher-risk populations in rural areas.

5.2.4. Limitations

There are a few study limitations. One of the main limitations to consider is the reliability of using Google Ads Keyword to draw conclusions about HZ. Cervellin et al. showed that patterns in Google trends search volume reflected more the media coverage of a disease than the actual epidemiological burden for common diseases with low media coverage and rare diseases with high media coverage, thereby only being modestly reliable in these cases (2017). As HZ would fall into the former category and studies using web search data to evaluate HZ are rare, further infodemiological research on HZ is needed to evaluate the reliability of such methodologies.

Additionally, Google does not provide demographic information about its search engine users with Google Ads Keyword Planner. Definitive conclusions cannot be drawn about the evaluated population. Specific demographic subgroups therefore cannot be studied using this method. The possible underrepresentation of elderly populations may be seen as a limitation of the study. However, the percentage of internet users among the elderly is continuously increasing so that this limitation may soon be negligible (ARD & ZDF, 2022). Restricting the preferred language to German may have also excluded data from resident populations that do not speak German. This may be particularly relevant for the German city states, which have the highest percentages of foreign residents among all residents for the German federal states (Statistisches Bundesamt, 2022).

Furthermore, the monthly search volumes are only estimates provided by the software's algorithm, with additional outside verification of the actual search volume not being possible. Despite 95% of the German population using Google as its preferred search engine, the possibility of a selection bias remains (StatCounter, 2022). Google's auto-fill function, whereby

more frequently searched for keywords are suggested as users type, may be a source of bias in search behavior. Finally, the findings only show associations and do not indicate any definitive causalities.

6. Conclusion

This study was able to demonstrate that a multisource approach to investigating a disease can provide a comprehensive overview of the disease burden and associated factors for HZ and PHN. While medical records are a valuable source of information for clinically relevant data like comorbidities, questionnaire data provide more insight into patient mental well-being and QoL. Overall, the study data indicated that individuals suffering from PHN are older and more likely to have multiple comorbidities while also showing that PHN negatively impairs everyday activities and mental health.

Similarly, web search data analysis, which has recently seen growing applications in disease monitoring and public health research, was able to demonstrate that HZ-related internet search volume has continuously increased during the study period and that regional factors like population and physician density influence search behavior (Kain et al., 2023). Of particularly interest was HZ with trigeminal involvement, possibly mirroring the increased burden of disease for these localizations. The overall increasing search volume underlines the relevance of the internet for health information when access to medical care may be limited. Especially since the disease incidence and share of older internet users are expected to grow, web search data can provide further insight into HZ to support targeted public health awareness programs in areas with unmet needs. Evaluating internet search volume has shown to be a promising method for assessing associated disease characteristics for HZ and can complement information collected in more traditional settings, like medical records and questionnaire data.

Based on the findings of the present study, future studies should investigate barriers to medical care to improve HZ prevention programs, as vaccination is the most effective method in mitigating the effects of HZ and its complications (Gross et al., 2020). Since several years have elapsed since the availability of HZ vaccines and vaccinations in general have been a topic of interest since the COVID-19 pandemic (Khakimova et al., 2022), web search data studies can also evaluate public interest in HZ vaccinations in Germany. Additionally, the relationship between PHN, QoL, and mental health should be investigated in further studies that include a more representative sample of HZ patients and use a prospective study design. Furthermore, future research should more thoroughly investigate the effects of PHI on HRQoL and mental health, as PHI remains a not well understood complication of HZ.

Overall, the disease burden for HZ and PHN is substantial and public interest in HZ is high. With an increasingly aging population, a better understanding of who is at risk for disease complications and how these diseases impair well-being can support targeted public health awareness campaigns as well as improve prevention strategies.

7. Summary

Herpes zoster (HZ) is a viral infectious disease caused by the reactivation of the varicella zoster virus and is characterized by a painful vesicular dermatomal rash (Strommen et al., 1988). Postherpetic neuralgia (PHN), a chronic pain syndrome, is the most common complication of HZ (Johnson & Rice, 2014) and can last years to a lifetime in worst cases (Beydoun, 1999). Both HZ and PHN have been associated with immense costs on healthcare systems as well as impairment of quality of life for affected individuals. With age being one of the primary risk factors for these two diseases, the burden of disease for HZ and PHN is expected to increase with an increasingly aging population (Ultsch et al., 2013). The aims of this study were to evaluate associated factors and the disease burden for HZ and PHN using data collected in a traditional clinical setting as well as internet search data.

In this study, questionnaires were distributed to patients who had been treated in- or outpatient for HZ at the department for dermatology and allergy of the university clinic of the Technical University of Munich. The questionnaire inquired, among others, about current pain severity to determine PHN status, current itch severity, mental health, smoking habits, and alcohol consumption habits. Medical records data, like disease localization, comorbidities, antiviral therapy duration, and acute HZ pain severity were also recorded for participants who were treated inpatient. To complement these data, a web search data analysis was conducted for the search terms “herpes zoster” and the German layman’s term for the disease, “Gürtelrose” using Google Ads Keyword Planner. Relevant keywords generated by the software were qualitatively assessed then classified thematically into eleven categories. The search volume over the four-year timeframe spanning October 2016 to September 2020 was evaluated. Correlations between search volume and population density, dermatologist density, and overall physician density were analyzed to identify possible geographic variations in search behavior.

The questionnaire data showed a PHN prevalence of 26.0% in the overall study population, which varied between 4.7% and 37.3% depending on participant ages. In analyses of group differences between participants with and without PHN using Mann-Whitney U tests, chi-square tests, or Fisher’s exact tests, differences were observed for current pain severity, interference of daily activities scores, neuropathic itch symptoms, current itch severity, mental health scores, and the number of comorbidities. A high positive correlation was observed between severity for the worst pain in the last 24 hours and pain-related interference of daily

activities (r_s = .84, p = < .001), and a moderate positive correlation was observed between pain-related interference and age (r_s = .241, p = <.001). Logistic regression analyses only considered data from the complete cases for the variables of interest, which demonstrated significant associations between PHN with age (aOR 1.07 [1.00-1.17], p = .040) and strongest itch severity (aOR 1.94 [1.43-1.95], p < .001) in multivariable Firth logistic regressions.

In the four-year study period from October 2016 to September 2020, a total of 20,816,210 searches, translating to 25,033 searches per 100,000 inhabitants, were conducted in Germany for the search terms “herpes zoster” and “Gürtelrose”. A total of 1,651 keywords were identified, of which general keywords had the highest search volume followed by those relating to disease *localization* and *symptoms and severity*. Search volume increased over time, although no seasonal patterns in search volume were observed. Correlations were observed between average monthly search volume and population density, dermatologist density, and physician density, with urban city-states demonstrating higher search volumes per 100,000 inhabitants.

Data from the questionnaire and medical records showed that participants with PHN were older and more likely to experience interference of their ability to perform daily activities. Mental health may also have been impaired because of PHN. Itch was strongly associated with PHN in the present study, which warrants further research on the topic of postherpetic itch. To complement this data, web search data analyses showed that the online interest in HZ is increasing and that disease localizations associated with higher disease burden, like HZ with trigeminal involvement, were of particular interest. Data analyzed from a variety of sources, including clinical and non-clinical data, may help improve HZ disease prevention strategies and targeted public health awareness campaigns by providing a more holistic overview of associated factors and disease burden.

8. References

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9. Appendix

9.1. Participant study information

Klinik und Poliklinik
für Dermatologie und Allergologie am Biederstein
des Klinikums rechts der Isar
der Technischen Universität München
Anstalt des öffentlichen Rechts
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Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein
TU München, Postfach 401 840, 80718 München

Max Mustermann
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80802 München

Analyse assoziierter Faktoren für das Auftreten von Komorbiditäten, Post-Zoster-Neuralgien und Rezidiven, sowie die subjektive Wahrnehmung der Erkrankung bei Gürtelrose Patienten – STOPZOS

Sehr geehrte Damen, sehr geehrte Herren,

wir möchten Sie fragen, ob Sie bereit sind, an unserer Studie teilzunehmen.

Die Gürtelrose zählt zu den häufigsten akuten Krankheiten in der Dermatologie. Etwa 350.000 – 400.000 Menschen in Deutschland werden jedes Jahr mit Gürtelrose diagnostiziert. Ziel dieser Studie ist, den Gesundheitszustand von Betroffenen nach einer Gürtelrose-Infektion und die daraus resultierenden möglichen Einschränkungen der Lebensqualität zu erfassen.

Da wir aus wissenschaftlichen Gründen an dem Befinden und der Lebensqualität von Gürtelrose Patienten interessiert sind, würden wir uns sehr freuen, wenn Sie den begleitenden Fragebogen beantworten. Durch Ihre Teilnahme helfen Sie uns dabei, Faktoren für das Auftreten von Begleiterkrankungen, anhaltende Nervenschmerzen (Post-Zoster-Neuralgien) und wiederkehrendes Auftreten zu identifizieren.

Für eine Studienteilnahme werden Sie gebeten einen kurzen Fragebogen (ca. 10-15 Minuten) auszufüllen und die Einwilligungserklärung zu unterschreiben, wenn Sie mit der Studienteilnahme einverstanden sind. Ihre Teilnahme an dieser Studie ist **freiwillig**. Sie werden in die Studie also nur dann einbezogen, wenn Sie dazu schriftlich Ihre Einwilligung erklären. Bei einer Teilnahme entstehen für Sie **keine zusätzlichen Kosten**.

Wir verpflichten uns zu einer strengen Einhaltung der Datenschutzbestimmungen. Alle erhobenen Daten werden unter strenger Beachtung des gesetzlichen Datenschutzes aufbewahrt und sind gegen unbefugten Zugriff gesichert.

Für Rückfragen stehen wir Ihnen gerne zur Verfügung. Über Ihre Mitarbeit würden wir uns sehr freuen.

Mit freundlichen Grüßen,

Priv.-Doz. Dr. Dr. med. Alexander Zink, MPH
Oberarzt

Cand. med. Alphina Kain
Doktorandin der Medizin

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Probandeninformation

Analyse assoziierter Faktoren für das Auftreten von Komorbiditäten, Post-Zoster-Neuralgien und Rezidiven, sowie die subjektive Wahrnehmung der Erkrankung bei Gürtelrose Patienten – STOPZOS

Sehr geehrte Damen, sehr geehrte Herren,

wir möchten Sie fragen, ob Sie bereit sind, an der nachfolgend beschriebenen Studie teilzunehmen. Die Studie wurde von der zuständigen Ethikkommission zustimmend bewertet und wird von der Hautklinik der Technischen Universität München (TUM) veranlasst, organisiert und durchgeführt. Ihre Teilnahme an dieser Studie ist **freiwillig**. Sie werden in die Studie also nur dann einbezogen, wenn Sie dazu schriftlich Ihre Einwilligung erklären. Bei einer Teilnahme entstehen für Sie **keine** zusätzlichen Kosten.

1. Warum wird diese Studie durchgeführt?
Die Gürtelrose (Herpes Zoster) zählt zu den häufigsten akuten Krankheiten in der Dermatologie. Etwa 350.000 – 400.000 Menschen in Deutschland werden jedes Jahr mit Gürtelrose diagnostiziert. Jeder zweite 85-Jährige hatte bereits mindestens einmal Gürtelrose. Aufgrund unserer älter werdenden Gesellschaft und der zunehmenden Anzahl immunsupprimierter Menschen, kann in Deutschland mit einer steigenden Häufigkeit von Gürtelrose gerechnet werden. Die vorliegende Studie untersucht Faktoren für (I) das Auftreten von Begleiterkrankungen, (II) anhaltende Nervenschmerzen (Post-Zoster-Neuralgien) und (III) wiederkehrende Gürtelrose-Infektionen (Rezidiven).

2. Wie ist der Ablauf der Studie und was muss ich bei Teilnahme beachten?
Für eine Studienteilnahme werden Sie gebeten einen kurzen Fragebogen (ca. 10-15 Minuten) auszufüllen und die Einwilligungserklärung zu unterschreiben, wenn Sie mit der Studienteilnahme einverstanden sind. Wir bitten Sie den **ausgefüllten Fragebogen mit der Einwilligungserklärung** anschließend im **mitgesandten und vorfrankierten Antwortkuvert zurückzusenden.**

3. Welchen persönlichen Nutzen habe ich von der Teilnahme an der Studie und gibt es Risiken?
Bei einer Studienteilnahme haben Sie keinen direkten persönlichen Nutzen. Durch Ihre Teilnahme helfen Sie uns jedoch dabei, die Faktoren für das Auftreten von Begleiterkrankungen, anhaltende Nervenschmerzen (Post-Zoster-Neuralgien) und wiederkehrende Gürtelrose-Infektion (Rezidiven) zu erfassen. Mit dem Fragebogen sollen neben Daten zur Person (Geschlecht, Alter, Familienstand, höchster Bildungsabschluss, Erwerbstatus, Einkommen), Fragen zu Schmerzen, Fragen zum Lebensstil, sowie Folge- oder Begleiterkrankungen der Gürtelrose abgefragt werden. Anhand standardisierter Fragebögen werden Ihre psychosoziale Belastung und physischen Einschränkungen dargestellt und somit werden auch die Auswirkungen der Krankheit auf Ihr soziale Leben erfasst.

I. **Es sollen Ansätze geschaffen werden, um die Lebensqualität und Alltagsaktivitäten von betroffenen Patienten zu verbessern und Risiken dieser schweren Dermatose vorzubeugen.**
II. **Es bestehen keinerlei gesundheitlichen Risiken für Sie bei einer Teilnahme.**

4. Erhalte ich eine Aufwandsentschädigung?
Es ist KEINE finanzielle Aufwandsentschädigung vorgesehen.

5. Hinweise zum Datenschutz
Für die Datenverarbeitung in dieser Studie ist verantwortlich:

Fakultät für Medizin der Technischen Universität München, vertreten durch den Dekan. Die Studie wird am Klinikum rechts der Isar der Technischen Universität München, Ismaninger Straße 22, 81675 München, durchgeführt.

Die Studie wird von PD Dr. Dr. med. Alexander Zink, MPH und Alphina Kain an der Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein durchgeführt

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Biedersteiner Str. 29 80802 München.

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Biedersteiner Str. 29 80802 München.

Den Datenschutzbeauftragten der Technischen Universität München erreichen Sie unter:
Behördlicher Datenschutzbeauftragter der Technischen Universität München
Postanschrift: Arcisstraße 21, 80333 München
Telefon: 089/289-17052
E-Mail: beauftragter@datenschutz.tum.de.

Rechtsgrundlage für die Verarbeitung Ihrer Daten ist Ihre Einwilligung nach Art. 6 Abs. 1 lit. a), insbesondere bei Gesundheitsdaten auch Art. 9 Abs. 2 lit. a) DS-GVO. Die Verarbeitung Ihrer Daten dient ausschließlich zum Zwecke der Durchführung und Auswertung der personenbezogenen Daten innerhalb der oben genannten Studie. Zu Ihren personenbezogenen Daten gehören personenidentifizierende Daten wie Name, Anschrift, Kontaktdaten sowie „sensible" personenbezogene Gesundheitsdaten. Alle unmittelbar Ihre Person identifizierende Daten [Name, Geburtsdatum, Anschrift, ...] werden durch einen **Identifizierungscode** ersetzt (pseudonymisiert). Dies **schließt eine Identifizierung Ihrer Person durch Unbefugte weitgehend aus.** Im Studienverlauf werden die hier erfassten Daten mit Krankheitsdate aus Ihrer Akte kombiniert. Sobald die geschehen ist, wird die Entschlüsselungsliste **unwiderruflich vernichtet**.

Es findet keine Übermittlung Ihrer personenbezogenen Daten in ein Drittland oder an eine internationale Organisation statt. Ihre Daten werden in der Klinik und Poliklinik für Dermatologie und Allergologie der Technischen Universität München gespeichert. Wir bewahren Ihre personenbezogenen Daten nur solange auf, wie dies für den oben genannten Zweck erforderlich ist. Ihre Daten werden nach Ablauf von **10 Jahren** gelöscht.

Sie haben das Recht, Auskunft über die Sie betreffenden Daten zu erhalten, auch in Form einer unentgeltlichen Kopie. Darüber hinaus können Sie die Berichtigung, Sperrung oder Löschung Ihrer Daten verlangen. Sie haben das Recht, Ihre Einwilligung jederzeit ohne Angabe von Gründen und ohne Nachteile für Sie zu widerrufen. Die Rechtmäßigkeit der aufgrund der Einwilligung bis zum Widerruf erfolgten Verarbeitung wird hiervon nicht berührt.

Wenden Sie sich in diesen Fällen an: publichealth.derma.med@tum.de

Bei Rückfragen zum Datenschutz wenden Sie sich bitte an den oben genannten Datenschutzbeauftragten. Sie haben ebenfalls das Recht, sich bei der Aufsichtsbehörde zu beschweren. Wenden Sie sich an:
Bayerischer Landesbeauftragter für den Datenschutz
Postanschrift: Postfach 22 12 19, 80502 München
Hausanschrift: Wagmüllerstraße 18, 80538 München
E-Mail: poststelle@datenschutz-bayern.de.

6. An wen wende ich mich bei weiteren Fragen?
Bei weiteren oder später auftretenden Fragen können Sie sich jederzeit an das Studienteam wenden.

Ihr Ansprechpartner:

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9.2. Questionnaire

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Analyse assoziierter Faktoren für das Auftreten von Komorbiditäten, Post-Zoster-Neuralgien und Rezidiven, sowie die subjektive Wahrnehmung der Erkrankung bei Gürtelrose Patienten – STOPZOS

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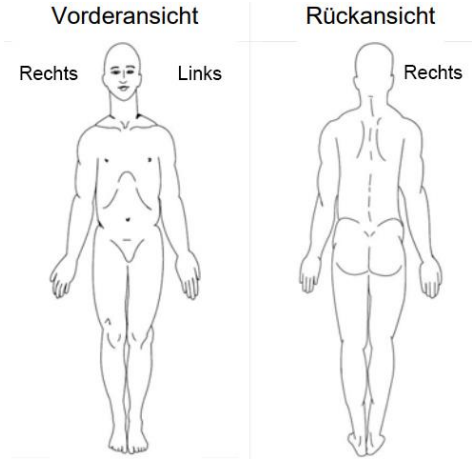
Vielen Dank, dass Sie an unserer Umfrage teilnehmen! Wir haben diesen Fragebogen im Rahmen einer Studie an der Technischen Universität München entworfen, um mehr über die physische und psychosoziale Belastung von Menschen mit Herpes Zoster (Gürtelrose) zu erforschen. Hierbei gibt es keine richtigen oder falschen Antwortmöglichkeiten. Bitte beantworten Sie alle Fragen offen und nach eigenem Empfinden. **Ihre Daten werden selbstverständlich vertraulich behandelt und NICHT an Dritte weitergegeben.** Das Ausfüllen des Fragebogens wird ca. 10-15 Minuten ihrer Zeit in Anspruch nehmen, wofür wir uns sehr herzlich bei Ihnen bedanken möchten!

Kurzes Zoster-Schmerzinventar (ZBPI)

Menschen mit Gürtelrose können in den vom Ausschlag befallenen Hautbereichen viele verschiedene Arten von Schmerzen oder Beschwerden verspüren. Diese Empfindungen können in den vom Ausschlag befallenen Hautbereichen auch nach dem Verschwinden des Ausschlags bestehen bleiben oder zurückkehren.
Bitte berücksichtigen Sie bei der Beantwortung der folgenden Fragen alle Arten von Schmerzen in den vom Ausschlag befallenen Hautbereichen, einschließlich jener Schmerzen, die durch einen Luftstrom auf der Haut, durch die Reibung der Kleidung auf der Haut oder durch Hitze oder Kälte ausgelöst werden.
Schmerzen oder Beschwerden, die nichts mit Ihrer Gürtelrose zu tun haben, wie z.B. Rückenschmerzen, Schmerzen aufgrund von Arthritis oder Kopfschmerzen sollen nicht miteinbezogen werden.

1. Hatten Sie in den letzten 24 Stunden Schmerzen, die durch Ihre Gürtelrose verursacht wurden?
○ Ja ○ Nein

2. Schraffieren Sie in nachstehender Zeichnung die Gebiete, in denen Sie Schmerzen haben. ***Markieren Sie die Stelle, die Sie am meisten schmerzt, mit „X".***



3. <u>Kreisen</u> Sie die Zahl ein, die Ihre *stärksten* Schmerzen in den letzten 24 Stunden am besten beschreibt:

0 1 2 3 4 5 6 7 8 9 10

keine Schmerzen — stärkste vorstellbare Schmerzen

4. <u>Kreisen</u> Sie die Zahl ein, die Ihre *geringsten* Schmerzen in den letzten 24 Stunden am besten beschreibt:

0 1 2 3 4 5 6 7 8 9 10

keine Schmerzen — stärkste vorstellbare Schmerzen

5. <u>Kreisen</u> Sie die Zahl ein, die Ihre *durchschnittlichen* Schmerzen in den letzten 24 Stunden am besten beschreibt:

0 1 2 3 4 5 6 7 8 9 10

keine Schmerzen — stärkste vorstellbare Schmerzen

6. <u>Kreisen</u> Sie die Zahl ein, die beschreibt, wie stark Ihre Schmerzen *in diesem Moment* sind:

0 1 2 3 4 5 6 7 8 9 10

keine Schmerzen — stärkste vorstellbare Schmerzen

7. Werden die *Schmerzen, die durch Ihre Gürtelrose verursacht werden*, behandelt (mit Medikamenten oder anderweitig)

○ Ja ○ Nein

8. Bitte denken Sie an die vergangenen 24 Stunden. Wie sehr wurden die *Schmerzen, die durch Ihre Gürtelrose verursacht wurden*, durch diese Behandlungen oder Medikamente <u>gelindert</u>? Bitte kreisen Sie die Prozentzahl ein, die am besten die Schmerzlinderung zeigt.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

keine Linderung — vollständige Linderung

9. Bitte <u>kreisen</u> Sie die Zahl ein, die angibt, wie stark die *Schmerzen, die durch Ihre Gürtelrose verursacht wurden*, Sie in den vergangenen 24 Stunden in den folgenden Bereichen *beeinträchtigt* haben:

A. Allgemeine Aktivität	0 keine Beeinträchtigung	1	2	3	4	5	6	7	8	9	10 vollständige Beeinträchtigung
B. Stimmung	0 keine Beeinträchtigung	1	2	3	4	5	6	7	8	9	10 vollständige Beeinträchtigung
C. Gehvermögen	0 keine Beeinträchtigung	1	2	3	4	5	6	7	8	9	10 vollständige Beeinträchtigung
D. Normale Arbeit (sowohl außerhalb des Hauses als auch Hausarbeit)	0 keine Beeinträchtigung	1	2	3	4	5	6	7	8	9	10 vollständige Beeinträchtigung
E. Beziehungen zu anderen Menschen	0 keine Beeinträchtigung	1	2	3	4	5	6	7	8	9	10 vollständige Beeinträchtigung
F. Schlaf	0 keine Beeinträchtigung	1	2	3	4	5	6	7	8	9	10 vollständige Beeinträchtigung
G. Lebensfreude	0 keine Beeinträchtigung	1	2	3	4	5	6	7	8	9	10 vollständige Beeinträchtigung

Neuropathische Schmerzen

Die ersten Fragen beziehen sich nur auf Spontanschmerzen, d.h. solche Schmerzen, die ohne äußere Auslöser auftreten.
Haben Sie **Spontanschmerzen**, d. h. Schmerzen, die ohne äußeren Auslöser auftreten?
Bitte kreuzen Sie für jede der folgenden Fragen die Ziffer an, die am besten der **Stärke Ihrer Spontanschmerzen im Mittel über die letzten 24 Stunden entspricht**. Kreuzen Sie „0" an, wenn Sie diese Art Schmerz nicht verspürt haben. (kreuzen Sie bitte immer nur eine Ziffer an)

Q1. Ist Ihr Schmerz brennend?

kein Brennen	0	1	2	3	4	5	6	7	8	9	10	schlimmstes vorstellbares Brennen

Q2. Fühlt sich Ihr Schmerz an wie eingeschnürt oder wie in einem Schraubstock eingeklemmt zu sein?

kein Einschnüren	0	1	2	3	4	5	6	7	8	9	10	schlimmstes vorstellbares Einschnüren

Q3. Fühlt sich Ihr Schmerz wie ein Druck an?

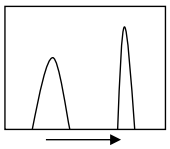
kein Druck	0	1	2	3	4	5	6	7	8	9	10	schlimmster vorstellbarer Druck

Q4. Wie lange dauerten Ihre Spontanschmerzen **in den letzten 24 Stunden**?
Kreuzen Sie die Antwort an, die der Dauer am besten entspricht:

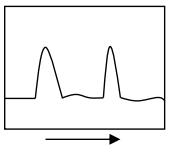
- dauerhaft (mehr als 12 Stunden) ☐
- zwischen 8 und 12 Stunden ☐
- zwischen 4 und 7 Stunden ☐
- zwischen 1 und 3 Stunden ☐
- weniger als 1 Stunde ☐

Schmerzattacken / unterbrochener Schmerz

Beschreibt eines der beiden Bilder die Schmerzen, wie Sie sie verspüren?



Schmerzattacken (unterbrochener Schmerz) dazwischen schmerzfrei



Schmerzattacken (unterbrochener Schmerz) auch dazwischen Schmerzen

Für jede der folgenden Fragen kreuzen Sie bitte die Ziffer an, die **am besten die mittlere Stärke Ihrer Schmerzattacken während der letzten 24 Stunden** angibt. Kreuzen Sie „0" an, wenn Sie einen solchen Schmerz nicht verspürt haben. (kreuzen Sie bitte immer nur eine Ziffer an)

Q5. Empfinden Sie Ihre Schmerzattacken wie elektrische Schläge?

überhaupt nicht	0	1	2	3	4	5	6	7	8	9	10	schlimmste vorstellbare elektrische Schläge

Q6. Fühlt sich Ihr Schmerz stechend an?

kein Stechen	0	1	2	3	4	5	6	7	8	9	10	schlimmstes vorstellbares Stechen

Q7. Wie viele dieser Schmerzattacken hatten Sie **in den letzten 24 Stunden**?
Wählen Sie die Antwort, die am ehesten zutrifft:

mehr als 20	☐
zwischen 11 und 20	☐
zwischen 6 und 10	☐
zwischen 1 und 5	☐
keine Schmerzattacken	☐

Haben Sie Schmerzen, die durch bestimmte Auslöser hervorgerufen oder verschlimmert werden, z. B. durch Reiben, Druck, oder Kontakt mit kalten Gegenständen im schmerzhaften Bereich?
Für jede der folgenden Fragen kreuzen Sie bitte die Ziffer an, die am besten der Stärke der Schmerzen, die durch Auslöser hervorgerufenen oder verschlimmerten entspricht, die Sie **im Mittel in den letzten 24 Stunden** hatten. Kreuzen Sie „0“ an, wenn Sie diesen Typ Schmerz nicht verspürt haben. (kreuzen Sie bitte immer nur eine Ziffer an)

Q8. Haben Sie im schmerzhaften Bereich Schmerzen, die durch Reiben hervorgerufen oder verschlimmert werden?

kein Schmerz	0	1	2	3	4	5	6	7	8	9	10	maximal vorstellbarer Schmerz

Q9. Haben Sie Schmerzen, die durch Druck auf den schmerzhaften Bereich hervorgerufen werden?

kein Schmerz	0	1	2	3	4	5	6	7	8	9	10	maximal vorstellbarer Schmerz

Q10. Haben Sie Schmerzen, die durch Kontakt mit einem kalten Gegenstand im schmerzhaften Bereich hervorgerufen oder verschlimmert werden?

kein Schmerz	0	1	2	3	4	5	6	7	8	9	10	maximal vorstellbarer Schmerz

Haben Sie **im schmerzhaften Bereich** ungewöhnliche Gefühlsstörungen?
Für jede der folgenden Fragen kreuzen Sie bitte die Ziffer an, die **am besten der Stärke Ihrer ungewöhnlichen Gefühlsstörungen** entspricht, die Sie **durchschnittlich in den letzten 24 Stunden** hatten. Kreuzen Sie „0“ an, wenn Sie dieses Gefühl nicht hatten (kreuzen Sie immer nur eine Ziffer an).

Q11. Empfinden Sie ein Kribbeln?

kein Kribbeln	0	1	2	3	4	5	6	7	8	9	10	maximal vorstellbares Kribbeln

Q12. Empfinden Sie etwas, das sich anfühlt wie Ameisenlaufen?

kein Ameisenlaufen	0	1	2	3	4	5	6	7	8	9	10	maximal vorstellbares Ameisenlaufen

Juckreiz

Auf einer Skala von 0 (kein Jucken) bis 10 (schlimmstes vorstellbares Jucken), wie war der Juckreiz durchschnittlich in den letzten 24 Stunden? Bitte nur eine Zahl ankreuzen

0	1	2	3	4	5	6	7	8	9	10

Auf einer Skala von 0 (kein Jucken) bis 10 (schlimmstes vorstellbares Jucken), wie war der Juckreiz am stärksten in den letzten 24 Stunden? Bitte nur eine Zahl ankreuzen

0	1	2	3	4	5	6	7	8	9	10

Wohlbefinden I

Die folgenden Aussagen betreffen Ihr Wohlbefinden in den letzten zwei Wochen. Bitte markieren Sie bei jeder Aussage die Rubrik, die Ihrer Meinung nach am besten beschreibt, wie Sie sich in den letzten zwei Wochen gefühlt haben.

In den letzten 2 Wochen:	**Die ganze Zeit**	**Meist-ens**	**Etwas mehr als die Hälfte der Zeit**	**Etwas wen-iger als die Hälfte der Zeit**	**Ab und zu**	**Zu keinem Zeit-punkt**
… war ich froh und guter Laune	o	o	o	o	o	o
… habe ich mich ruhig und entspannt gefühlt	o	o	o	o	o	o
… habe ich mich energisch und aktiv gefühlt	o	o	o	o	o	o
… habe ich mich beim Aufwachen frisch und ausgeruht gefühlt	o	o	o	o	o	o
… war mein Alltag voller Dinge, die mich interessieren	o	o	o	o	o	o

Wohlbefinden II

Kreuzen Sie bitte jeweils 1 Antwortmöglichkeit an

Wie oft fühlten Sie sich im Verlauf der **letzten 2 Wochen** durch die folgenden Beschwerden beeinträchtigt?	**Nie**	**An manchen Tagen**	**An mehr als der Hälfte der Tage**	**Beinahe jeden Tag**
Gefühle der Nervosität, Ängstlichkeit oder Anspannung	o	o	o	o
Unfähigkeit, Sorgen zu stoppen oder zu kontrollieren	o	o	o	o
Übermäßige Sorgen bezüglich verschiedener Angelegenheiten	o	o	o	o
Schwierigkeiten zu entspannen	o	o	o	o
So rastlos sein, dass das Stillsitzen schwer fällt	o	o	o	o
Schnelle Verärgerung oder Gereiztheit	o	o	o	o
Angstgefühle, so als könnte etwas Schreckliches passieren	o	o	o	o

Zigaretten

Wie oft rauchen Sie? **Und wieviel?**	○ nie ○ selten ○ täglich, aber weniger als 1 Schachtel/Tag ○ ca. 1 Schachtel/Tag ○ ca. 1,5 Schachteln/Tag ○ ca. 2 Schachteln/Tag ○ mehr als 2 Schachteln/Tag **(1 Schachtel = 20 Zigaretten)** **Falls zutreffend:** Seit wann rauchen Sie? _____ Jahre **Falls Sie Ex-Raucher sind:** Wann haben Sie endgültig mit dem Rauchen aufgehört? _____ (Monat)/ _____ (Jahr) Wie lange haben Sie insgesamt geraucht? _____ Jahre

Alkohol

Wie oft und wie viele Gläser pro Mal trinken Sie Alkohol? *[1 Glas = 1 Flasche Bier/Most = 1/4 Wein/Sekt = 1 Schnaps (2 cl.)]*	○ nie ○ 2 x pro Monat oder seltener ○ 2 – 4 x pro Monat ○ 2 – 3 x pro Woche ○ 4 x pro Woche oder mehr	Nur zu beantworten, wenn Sie Alkohol trinken ○ 2 – 4 x pro Monat ○ 1 – 2 Gläser ○ 3 – 4 Gläser ○ 5 – 6 Gläser ○ 7 – 9 Gläser ○ 10 oder mehr
Hatten Sie jemals das Gefühl, Sie sollten Ihren Alkoholkonsum einschränken?	○ Ja	○ Nein
Wurden Sie jemals wegen Ihres Alkoholkonsums kritisiert und ärgerten sich darüber?	○ Ja	○ Nein
Fühlten Sie sich jemals schuldig wegen Ihres Alkoholkonsums?	○ Ja	○ Nein
Haben Sie jemals als erstes am Morgen Alkohol getrunken, um Ihre Nerven zu beruhigen oder um einen Kater loszuwerden?	○ Ja	○ Nein

Computerspiel- und Internetkonsum

An wie vielen Tagen pro Woche nutzen Sie aus privaten Gründen das Internet?	○ <1x pro Woche ○ ____ Tage pro Woche

Wie viele Stunden sind Sie üblicherweise an einem Tag im Internet?

○ weniger als 1 Stunde ○ 1 Stunde ○ 2 Stunden ○ 3 Stunden
○ 4 Stunden ○ 5 Stunden ○ 6 Sunden ○ 7 Stunden oder mehr

Bitte kreuzen Sie im Fragebogen die für Sie zutreffende Antwort an. Es gibt keine richtigen oder falschen Antworten, es zählt allein Ihre Einschätzung. Unter Internetnutzung wird auch der Zugang über Tablets, Smartphones oder andere internetfähige Geräte verstanden.

Wie oft…	Nie	Selten	Manch-mal	Häufig	Sehr häufig
... fällt es Ihnen schwer, die Internetsitzung zu beenden, wenn Sie online sind?	○	○	○	○	○
... sagen Ihnen Andere (z.B. Partner, Freunde, Familie), Sie sollten das Internet weniger häufig nutzen?	○	○	○	○	○
... sind Sie wegen Ihrer Internetnutzung unausgeschlafen?	○	○	○	○	○
... vernachlässigen Sie Ihre täglichen Verpflichtungen (Studium, Arbeit, Freunde), weil Sie lieber online gehen?	○	○	○	○	○
... gehen Sie online wenn Sie sich bedrückt fühlen?	○	○	○	○	○

Fragen zu Ihrer Person

Alter in Jahren:	___ Jahre
Geschlecht:	☐ weiblich ☐ männlich ☐ divers
Familienstand:	☐ ledig ☐ verheiratet ☐ geschieden ☐ getrennt lebend ☐ verwitwet
Haben Sie Kinder?:	☐ nein ☐ ja, ____ Kinder (Anzahl)
Höchster Bildungsabschluss:	☐ kein Schulabschluss ☐ Grund/Hauptschulabschluss ☐ Realschule (Mittlere Reife) ☐ Gymnasium (Abitur) ☐ Abgeschlossene Ausbildung ☐ Fachhochschulabschluss ☐ Hochschule
aktueller Erwerbsstatus:	☐ Schüler/in, Student/in oder Azubi ☐ Beamter/in ☐ Facharbeiter/in ☐ Rentner/in ☐ Angestellte/r ☐ Hausfrau/Hausmann ☐ Arbeitslos ☐ Selbstständig als_____ (bitte ausfüllen) ☐ anderer Beruf/ Status: _____

Datum

Bitte tragen Sie das aktuelle Datum als TT/MM/JJJJ ein

__ __ / __ __ / __ __ __ __

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