Comprehensive Review

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A systematic review and meta-analysis of risk factors for postherpetic neuralgia

Harriet J. Forbes*, Sara L. Thomas, Liam Smeeth, Tim Clayton, Ruth Farmer, Krishnan Bhaskaran, Sinéad M. Langan

Abstract

Patients with herpes zoster can develop persistent pain after rash healing, a complication known as postherpetic neuralgia. By preventing zoster through vaccination, the risk of this common complication is reduced. We searched MEDLINE and Embase for studies assessing risk factors for postherpetic neuralgia, with a view to informing vaccination policy. Nineteen prospective studies were identified. Meta-analysis showed significant increases in the risk of postherpetic neuralgia with clinical features of acute zoster including prodromal pain (summary rate ratio 2.29, 95% confidence interval: 1.42-3.69), severe acute pain (2.23, 1.71-2.92), severe rash (2.63, 1.89-3.66), and ophthalmic involvement (2.51, 1.29-4.86). Older age was significantly associated with postherpetic neuralgia; for individual studies, relative risk estimates per 10-year increase ranged from 1.22 to 3.11. Evidence for differences by gender was conflicting, with considerable between-study heterogeneity. A proportion of studies reported an increased risk of postherpetic neuralgia with severe immunosuppression (studies, n = 3/5) and diabetes mellitus (n = 1/4). Systemic lupus erythematosus, recent trauma, and personality disorder symptoms were associated with postherpetic neuralgia in single studies. No evidence of higher postherpetic neuralgia risk was found with depression (n = 4) or cancer (n = 5). Our review confirms a number of clinical features of acute zoster are risk factors for postherpetic neuralgia. It has also identified a range of possible vaccine-targetable risk factors for postherpetic neuralgia; yet aside from age-associated risks, evidence regarding risk factors to inform zoster vaccination policy is currently limited.

Keywords: Herpes zoster, Postherpetic neuralgia, Epidemiology, Risk factors

1. Introduction

Postherpetic neuralgia (PHN) is pain after an acute episode of herpes zoster (commonly known as shingles) continuing beyond rash healing.[16] The pain has been described as a constant burning or stabbing sensation, and some individuals experience allodynia (pain triggered from light contact with nonpainful stimuli).[47] Symptoms can persist for months or even years, and the condition can profoundly affect a patient's quality of life.[12,24] PHN is the most common complication of zoster; an estimated 12.5% of patients with zoster aged ≥50 years have PHN 3 months after zoster onset, and the proportion affected increases sharply with age.

Postherpetic neuralgia is often refractory to treatment.[10,20,40] Despite decades of research, evidence for the efficacy of administering antivirals at first appearance of the rash in reducing PHN incidence is unconvincing.[7] However, an effective live-attenuated vaccine is now available providing protection against zoster and might be used to protect those most likely to develop PHN and other complications of zoster.[30,36] Apart from age, other often reported risk factors for PHN relate largely to characteristics of the acute zoster episode, particularly, the severity of acute pain and rash at initial zoster presentation; however, the evidence has not been systematically reviewed.[14,31,32,42,48] Furthermore, as these are not vaccine-targetable, there is interest in identifying risk factors for PHN, which can be identified before the zoster episode, to inform zoster vaccination policy.

This article aims to systematically collate and summarise the epidemiological literature on risk factors for PHN including clinical features of acute zoster and those which are "vaccine-targetable."

2. Methods

2.1. Study selection

2.1.1. Search terms

We searched all published journal articles in MEDLINE and Embase between 1950 and February 3, 2014. We searched for articles containing PHN terms and risk factor analysis terms (Box 1 for full details). The search strategy used both subject heading and text word searches. Initial search terms were updated after searching the reference lists of relevant articles. To capture relevant grey literature, the New York Academy of Medicine Grey Literature Report (www.greylit.org), the Electronic Theses Online Service through the British Library (http://ethos.bl.uk), and the ISI Conference Proceedings Citation Index

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(http://isknowledge.com) were searched for the terms: "PHN" or "postherpetic neuralgia" or "postherpetic neuralgia," within the keywords or title (Box 1).

Box 1

Search terms used.

Medline:
[{ ("Postherpetic neuralgia"[exploded MeSH] OR PHN[Title or abstract] OR "postherpetic neuralgia"[Title or abstract] OR "post herpetic neuralgia"[Title or abstract] OR post-herpetic neuralgia[Title or abstract] OR "postherpetic pain"[Title or abstract] OR "post herpetic pain"[Title or abstract] OR post-herpetic pain [Title or abstract] OR (("Neuralgia"[exploded MeSH] OR "Pain"[exploded MeSH] OR neuralgia [Title or abstract] OR pain [Title or abstract]) AND ("Herpes zoster"[exploded MeSH] OR zoster[Title or abstract] OR shingles[Title or abstract] OR zona[Title or abstract] OR VZV[Title or abstract]))
AND ("Risk factors"[exploded MeSH] OR "Epidemiologic studies"[exploded MeSH] OR "Odds ratio"[exploded MeSH] OR "Multivariate analysis"[exploded MeSH] OR "Logistic Models"[exploded MeSH] OR "Prevalence"[exploded MeSH] OR "Incidence"[exploded MeSH] OR "odds ratio"[Title or abstract] OR "risk ratio"[Title or abstract] OR "relative risk"[Title or abstract] OR "risk factor"[Title or abstract] OR risk[Title or abstract] OR predict*[Title or abstract] OR correlat*[Title or abstract] OR etiol*[Title or abstract] OR aetiol*[Title or abstract] OR prevalence[Title or abstract] OR incidence[Title or abstract] OR rate*[Title or abstract]) }
OR "Postherpetic neuralgia/etiology"[exploded MeSH]
OR (("Neuralgia/etiology"[MeSH] OR "Pain/etiology"[MeSH]) AND (herpes zoster[exploded MeSH] OR "zoster"[Title or abstract] OR "shingles"[Title or abstract] OR "zona"[Title or abstract] OR "VZV"[Title or abstract]))]
AND "Humans"[MeSH]; limited to articles in language: ENGLISH
Embase:
[{ ("Postherpetic neuralgia"[exploded subject heading] OR "PHN"[Title or abstract] OR "postherpetic neuralgia"[Title or abstract] OR "post herpetic neuralgia"[Title or abstract] OR "post-herpetic neuralgia"[Title or abstract] OR "postherpetic pain"[Title or abstract] OR "post herpetic pain"[Title or abstract] OR post-herpetic pain [Title or abstract] OR (("Neuralgia"[exploded subject heading] OR "Pain"[exploded subject heading] OR "neuralgia" [Title or abstract] OR "pain" [Title or abstract]) AND (herpes zoster[exploded subject heading] OR "zoster"[Title or abstract] OR "shingles"[Title or abstract] OR "zona"[Title or abstract] OR "VZV"[Title or abstract]))
AND ("Risk factor"[exploded subject heading] OR "Epidemiology"[exploded subject heading] OR "Odds ratio"[exploded subject heading] OR "Multivariate analysis"[exploded subject heading] OR "Statistical model"[exploded subject heading] OR "Prevalence"[exploded subject heading] OR "Incidence"[exploded subject heading] OR "odds ratio" OR "risk ratio" OR "relative risk" OR "risk factor" OR "risk" [Title or abstract] OR "risk factor"[Title or abstract] OR "predict*"[Title or abstract] OR "correlat*"[Title or abstract] OR "etiol*"[Title or abstract] OR "aetiol*"[Title or abstract] OR "prevalence"[Title or abstract] OR "incidence"[Title or abstract] OR "rate*"[Title or abstract]) }
OR "Postherpetic neuralgia/etiology"[exploded subject heading]
OR (("Neuralgia/etiology"[subject heading] OR "Pain/etiology"[subject heading]) OR (herpes zoster[exploded subject heading] OR "zoster"[Title or abstract] OR "shingles"[Title or abstract] OR "zona"[Title or abstract] OR "VZV"[Title or abstract]))]
AND "Humans"[subject heading]; limited to language: ENGLISH
Grey literature:
New York Academy of Medicine Grey Literature Report: PHN OR postherpetic neuralgia OR title:(postherpetic AND neuralgia) OR title:PHN
ISI Conference Proceedings Citation Index: [{TS=(PHN or "postherpetic neuralgia" or "post herpetic neuralgia") AND TS=(risk or epidem* or "odds ratio" or rate)} OR {TI=(PHN or "postherpetic neuralgia" or "post herpetic neuralgia")}] AND TI=(risk or epidem* or "odds ratio" or rate) AND LANGUAGE: (English).
Note: In both databases the subject heading terms are arranged in a hierarchy with more specific linked subheadings arranged beneath wider terms. Exploding a subject heading indicates that the search includes all results below that heading.

2.2. Inclusion and exclusion criteria

Criteria were developed in an iterative process after preliminary searches. We included studies based on original data from analytical epidemiological studies, among adults (18 years+) with zoster. Postherpetic neuralgia had to be a study outcome and an age-adjusted effect estimate was required. We included risk factors, which were either (1) clinical features of the acute zoster episode or (2) vaccine-targetable, defined as risk factors identifiable before the onset of the zoster rash. Studies assessing only age as a risk factor were required to treat age as a continuous exposure (ie, linear on a log scale) such that its effects on PHN risk could be reported per 10-year increase. Studies assessing genes as risk factors for PHN were not required to have an age-adjusted effect measure, because allele frequencies are not typically associated with age.

We omitted studies assessing antiviral therapy as a determinant of PHN as they have been recently summarised in a Cochrane Systematic Review[7]; we also omitted studies assessing other PHN treatments (such as acupuncture and corticosteroids). We excluded studies examining risk factors for PHN within a general population sample (where patients with PHN were compared with non-zoster controls) because the risk of PHN in the general population comprises 2 parts; first, the risk of zoster and second, the risk of developing PHN among those with zoster. In these studies, it is impossible to disentangle whether any identified risk factors are simply predictive of zoster itself, or whether they are specifically risk factors for getting PHN. We also excluded studies restricted to specific clinical subgroups of patients with zoster, such as individuals with HIV, because their risk factors for PHN may differ. We restricted to English articles only; however, we did not place any restriction on study location or publication status.

2.3. Selecting studies

The titles and abstracts of all identified articles were assessed. If a study was deemed to potentially fulfil the inclusion criteria, full-text versions were retrieved and assessed. Reference lists of all retrieved articles were searched. To assess how reliably the study eligibility criteria were applied, a second author (R.F.) applied the inclusion criteria to a random 10% sample of all articles, and agreement between the primary allocation and the sample allocation was tested using Cohen's kappa statistic.[29] A kappa score of 1 denotes full agreement, and kappa values greater than 0.75 indicate excellent agreement.[44]

2.4. Data extraction

Extraction tables were piloted by S. L. Thomas and H. J. Forbes and then applied to remaining studies. Data (listed in Appendix, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132) were extracted by H. J. Forbes for each study. Authors were contacted for missing information (see appendix for template e-mail to corresponding authors, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132). When individual studies used multiple definitions of PHN, results classifying PHN as pain at 3 months after zoster onset (or that closest to 3 months) were extracted for the main analysis, as this is the most widely used definition of PHN.[12,17,30,36,45] Results from other PHN definitions were extracted for the Appendix (available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132).

2.5. Assessing risk of bias

The risk of bias assessment was based on the Cochrane Collaboration approach, in which each study is assessed separately for prespecified bias domains (see Appendix for further details available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132).

We also considered the validity of each study based on the sampling of patients with zoster, numbers declining to participate, and their characteristics, particularly the percentage developing PHN.

2.6. Data analysis

When at least 2 studies were deemed to be capturing the same risk factor within similar populations, we assessed between-study heterogeneity using the Cochrane Q statistic and the I^2 statistic, with $I^2 > 50\%$ used as a threshold indicating moderate heterogeneity. In the absence of heterogeneity, we planned to combine the estimates and produce a summary relative risk using fixed effects meta-analysis. However, for some risk factors, there was significant between-study statistical heterogeneity; therefore, we performed posthoc analysis to help ascertain the possible reasons for heterogeneity. This included rerunning the meta-analysis removing studies at high risk of bias and comparing I^2 values between clinical and methodological subgroups to evaluate potential sources of heterogeneity.[22] For this latter analysis, summary estimates from subgroups were formally compared using meta-regression; we compared subgroups according to (1) mean age of the study population (≥60 years vs <60 years), (2) definition of PHN (pain at 4 months vs pain at 3 months), (3) ascertainment of PHN (self-reported vs ascertained from medical records), (4) whether immunosuppressive patients were included or excluded, and (5) sources of study population (primary care vs other).

We also created a funnel plot to determine the risk of publication bias; gender was the only risk factor assessed in sufficient studies to be suitable for assessment (age effects were reported in different units making it unsuitable). The odds ratios (OR), representing the effect estimate of gender on PHN, were plotted against the standard error of the log odds,[41] representing the precision of the estimate, and symmetry was assessed visually (as there were too few studies to perform a formal test).[43] Statistical analyses were performed in STATA (version 13.1).

3. Results

The initial search identified 3614 articles. After removing duplicates, 2559 titles and abstracts were screened. Of these, 116 full-text articles were retrieved, 19 of which were included in the review (**Fig. 1**). Excluded studies are listed in the Appendix (Table A1), available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132.

Agreement between reviewers over the application of the inclusion criteria was very good (kappa score, 0.88). From the 10% sample of articles double screened, 1 study was not agreed on; the second reviewer initially selected this study[11] for inclusion; however, both reviewers subsequently agreed this extra article replicated a study already selected.[13]

3.1. Study characteristics and findings

Study characteristics are described in **Table 1**. There were 18 cohort studies and 1 case-base study (a modified case–control study, where the risk ratio is estimated by sampling controls from those at risk at the start of follow-up).[39] Study sizes ranged from 55 to 34,280, and 17/19 studies had less than 1000 participants at baseline. Zoster diagnoses were predominantly based on clinical opinion. Definitions of PHN were presence of pain 3 months after rash onset in 10 studies, although other definitions from 1 to 6 months were used. The percentage of patients with zoster developing PHN ranged from 2.6% to 67.3%. Mean age of study participants (available in 9 studies) ranged from 52.3 to 67.7 years. Studies were all from high-income countries.

Study findings are summarised in **Table 2** and **Figures 2 and 3**. Data were collected on clinical features of the acute episode including pain (15), rash extent and location (14), rash duration (9), sensory dysfunction (3), and other clinical features (11), and also vaccine-targetable risk factors including age and gender (18 studies), severe immunosuppression (5), other physical comorbidities such as autoimmune conditions (4), diabetes (6), cancer (5), recent physical trauma (1), psychological comorbidities (4), and other risk factors (9).

3.2. Clinical features of acute zoster episode as risk factors

3.2.1. Pain

3.2.1.1. Prodrome

Eleven cohort studies and the case-base study collected data on prodromal pain, ie, pain appearing before rash onset. Seven included prodromal pain in the final age-adjusted model and 5 reported effect estimates, with each giving a point estimate above 1. We obtained a pooled effect estimate of 2.29, 95% confidence interval (CI): 1.42 to 3.69 ($P_{heterogeneity} = 0.716$; $I^2 = 0.0\%$) in fixed effect meta-analysis. A cohort study among 533 immunocompetent patients reported a shorter prodrome (≤3 days) before rash onset was associated with reduced risk of PHN (adjOR: 0.49, 95% CI: 0.24-0.99).

3.2.1.2. Severe acute pain during zoster

Twelve cohort studies investigated severe acute pain as a risk factor for PHN. Although definitions of severe acute pain varied among studies, eg, pain scoring ≥4 using the Neuropathic Pain Questionnaire[5] and pain scoring ≥5 on the Visual Analogue Scale,[9] 8 reported it as a binary variable enabling us to pool estimates; there was good evidence that severe acute pain was associated with increased risk of PHN (rate ratio [RR]: 2.23, 95% CI: 1.71-2.92, $P_{heterogeneity} = 0.649$; $I^2 = 0.0\%$).

3.2.1.3. Allodynia

Allodynia was investigated in 3 cohort studies. One study reported a greater than 4-fold increased risk of PHN with brush (adjOR: 5.89, 95% CI: 1.50-23.1) and stretch-evoked allodynia (adjOR: 4.13, 95% CI: 0.98-17.50)[19]; however, small numbers (N = 93) led to wide CIs. A study among hospital patients treated in a pain clinic found no effect of allodynia (definition unclear; adjOR: 0.82, 95% CI: 0.24-2.81), whereas a final cohort study similarly reported no evidence of effect.[5,26] A summary estimate was not calculated because of the varying definitions of allodynia.

3.2.1.4. Pain interferes with daily functioning

Pain interfering with daily functioning at zoster onset was assessed in 3 cohort studies. The first, among 1358 individuals, reported a 1-unit increase in zoster brief pain inventory interference score was associated with 18% increase in PHN risk (adjOR: 1.18, 95% CI: 1.05-1.31).[13] Two other cohort studies reported binary (yes or

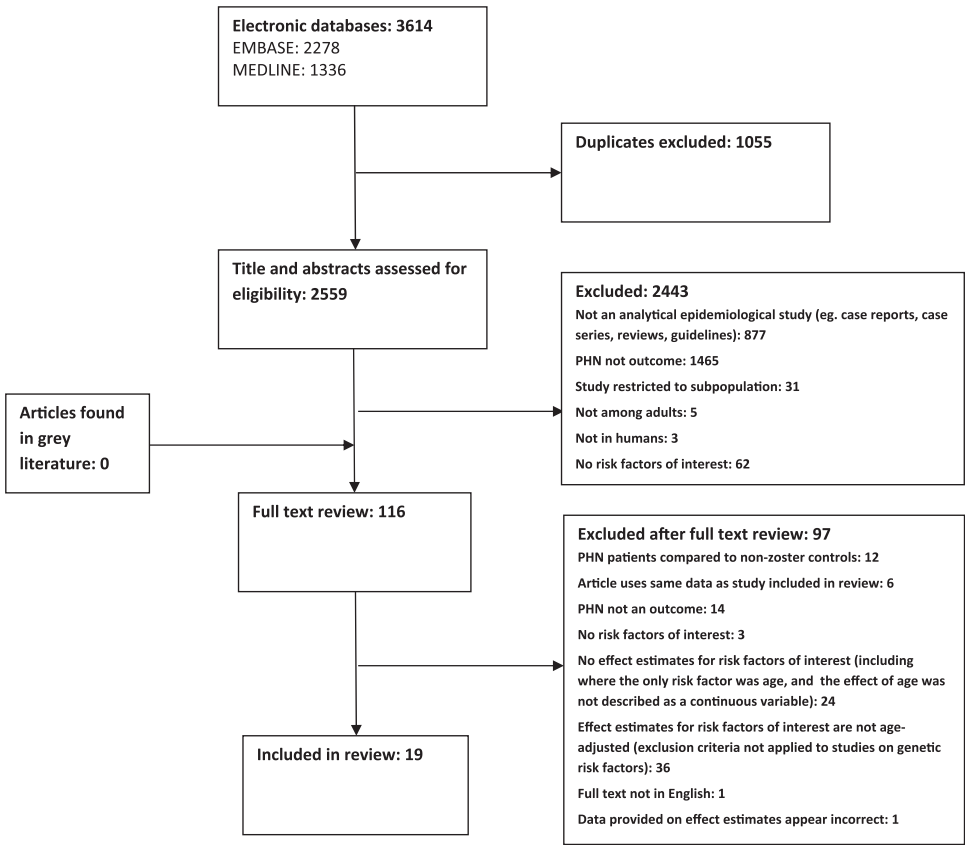

Figure 1. Flow diagram describing study selection.

no) data on pain interference. One found over 2-fold increased risk,[27] whereas the other found no evidence of association; the summary estimate of these 2 studies suggested there was strong evidence that pain interfering with daily functioning was associated with PHN (summary RR: 2.10, 95% CI: 1.27-3.48).

3.2.2. Rash severity and location

3.2.2.1. Severe rash

Rash severity data were collected in 8 studies. Five included it in their final age-adjusted model (although one did not report an OR); when combined in meta-analysis, severe rash was strongly associated with PHN risk (summary RR: 2.63, 95% CI: 1.89-3.66, $P_{heterogeneity} = 0.892$; $I^2 = 0.0\%$).

3.2.2.2. Ophthalmic involvement

A total of 13 studies recorded information on zoster location. Only 3 studies reported an effect estimate for ophthalmic involvement. Each of these 3 studies reported a point estimate above 1, yet the CIs crossed 1. When combining in a meta-analysis, there was evidence that ophthalmic zoster was associated with over twice the risk of PHN, compared with nonophthalmic zoster (summary RR: 2.51, 95% CI: 1.29-4.86, $P_{heterogeneity} = 0.782$; $I^2 = 0.0\%$).

3.2.3. Rash duration at presentation

Longer rash duration at presentation of zoster showed some evidence of being associated with reduced risk of PHN. A study on 598 immunocompetent patients showed for everyday the rash was present since presentation in primary care; there was over 20% reduced risk of PHN (adjOR: 0.78, 95% CI: 0.64-0.97).[35] Three other cohort studies estimated the risk of PHN for everyday from onset to diagnosis; point estimates were all below 1 (yet CIs were wide).[9,25,27] The summary estimate from meta-analysis showed a small reduction in PHN risk with everyday since rash onset (0.93, 95% CI: 0.86-0.99).

3.2.4. Other

One study assessed pinprick hypaesthesia (or numbness) as a risk factor for PHN: it was associated with a 7-fold increased risk of PHN (adjOR: 7.72, 95% CI: 2.00-29.90).

3.3. Vaccine-targetable risk factors

3.3.1. Age

Eighteen studies assessing the effects of age showed an increased risk of PHN with greater age. When possible, we summarised the effect of a 10-year increase in age on PHN risk (n = 9). The point estimates ranged from 1.22 to 3.11 per 10 years; the meta-analysis showed strong evidence of between-study heterogeneity ($P_{heterogeneity} = 0.029$; $I^2 = 55.1\%$). A small study (N = 249) showing an increased risk of PHN with a 10-year increase in age (adjRR: 1.22, 95% CI: 1.00-1.48) was excluded from the meta-analysis as the effect was reported as a risk ratio. In posthoc analysis, there was some weak evidence that the effect of age was associated with age of the study population (*P* value from meta-regression = 0.08; specifically the effect of age on PHN risk seemed higher in studies where the mean age was ≥60

Table 1

Studies assessing vaccine-targetable risk factors for postherpetic neuralgia nested within a population of patients with zoster: study characteristics.

Cohort studies

First author publication year	Country, year of study	Study population	Study size	Mean (SD) age in years at baseline	Outcome	Patients with PHN, n (%)	Definition and method of identifying zoster	Definition and method of ascertaining PHN	Method of ascertaining risk factor(s)	Risk factors assessed	Statistical analysis
Asada et al.[2]	Japan, 2008-2010	Patients with acute zoster registered in a cohort study on VZV immunity; aged ≥50 y	258 recruited 247 analysed 11 lost to follow-up	Not reported	PHN at 3 mo after zoster	32 (13.0)	Notified during telephone follow-up and confirmed through evaluation of clinical symptoms by 3 dermatologists and PCR	Pain 3 mo after rash onset Telephone survey to ascertain pain status by secretariat members.	Survey forms and examination by dermatologists	Age, gender, history of zoster, state of VZV-specific cell-mediated immunity (using VZV skin test reaction: no oedema formation and <5 mm diameter of red skin indicated weaker VZV-specific cell-mediated immunity)	Logistic regression
Bouhassira et al.[5]	France, 2007-2008	Patients presenting to General Practitioners (GPs) years with acute zoster; aged ≥50 y	1358 recruited 1091 analysed 267 lost to follow-up	67.7 (10.7)	PHN at 3 mo after zoster	127 (11.6)	Physician diagnosis within 7 d of rash onset, no history of zoster within previous 12 mo	Pain 3 mo after rash onset Telephone interview, using question, "Do you still have pain associated with your shingles?"	Physician interview and patient completed questionnaire at zoster diagnosis	Age, gender, family situation, living arrangements, delay in diagnosis, associated disease (undefined), average pain intensity, pressure allodynia, brush-evoked allodynia, global DN4 score, NPSI score, ZBPI interference score, SF-12 physical and mental component score, HADS score, and analgesic treatment	Logistic regression
Cebrián-Cuenca et al.[6]	Spain, 2006-07	Convenience sample of patients with acute zoster from 25 general practitioners; aged >14 y	146 recruited 124 analysed 22 lost to follow-up 16 declined to participate	Median 63.5 (range: 19-94)*	PHN at 3 mo after zoster	18 (14.5)	Physician diagnosis of zoster	Pain 3 mo after rash onset. Telephone/home interview by study investigators	Interview with patients and review of medical records	Age, gender, prodromal pain, extremities localization, sacrum localization, time between symptom onset and clinical diagnosis, time between rash onset and clinical diagnosis, antiviral use	Logistic regression
Coen et al.[9]	England, 1998-2001	Patients presenting to primary care with acute zoster; any age	280 recruited 272 analysed 8 lost to follow-up	Not reported (range 0-99)	PHN at 3 mo after zoster	52/250 (20.8)	Physician diagnosis within 7 d of rash, referred to 2 investigators for clinical and PCR or IFA confirmation	VAS score ≥3.3 mo after rash onset Follow-up visit or telephone interview with research nurse	Physician interview at enrolment	Age, gender, prodromal pain, extent of rash, time from onset of rash, ophthalmic branch involvement, pain severity using VAS	Logistic regression

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Table 1 (*continued*)

Cohort studies											
First author publication year	**Country, year of study**	**Study population**	**Study size**	**Mean (SD) age in years at baseline**	**Outcome**	**Patients with PHN, n (%)**	**Definition and method of identifying zoster**	**Definition and method of ascertaining PHN**	**Method of ascertaining risk factor(s)**	**Risk factors assessed**	**Statistical analysis**
Drolet et al.[12]	Canada, 2005-2006	Immunocompetent patients presenting to general practice or specialist centres, with zoster; aged ≥50 y	249 recruited all analysed	65.6 (10.8)	PHN at 3 mo after zoster	56 (22.5)	Physician diagnosis within 14 d of rash onset. Physicians received training on zoster diagnosis and their first 3 patients were confirmed by PCR	Severe pain 3 mo after rash onset Patient completed pain questionnaire at patients home	Physician interview and patient completed questionnaire at zoster diagnosis	Age, gender, education, working, income, has other pain condition, EQ-5D health status score before and during zoster in 5 domains: mobility, self-care, usual activities, having pain/discomfort, being anxious/depressed (rated none, some, or severe problems), VAS score before and during zoster, delay between recruitment and rash onset, dermatome affected, number of lesions, worst pain, prodrome, duration of prodrome, worse prodromal pain, reported pain interference score, antiviral treatment and timing of antiviral treatment, other medications. Immune suppressed patients (using high-dose oral corticosteroids or other immunosuppressive drugs, having invasive cancer or HIV/AIDS) included in sensitivity analysis	Log-binomial regression

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Table 1 (*continued*)

Cohort studies

First author publication year	Country, year of study	Study population	Study size	Mean (SD) age in years at baseline	Outcome	Patients with PHN, n (%)	Definition and method of identifying zoster	Definition and method of ascertaining PHN	Method of ascertaining risk factor(s)	Risk factors assessed	Statistical analysis
Haanpaa, 2000[19]	Finland, year not given	Primary care zoster patients without immunosuppression, psychiatric illness, substance abuse, systemic, or metabolic disease, neurologic disease influencing somatosensory testing; any age	113 recruited 93 analysed	58 (17.2)	PHN at 3 mo after zoster	28 (25)	Physician diagnosis	Pain 3 mo after rash onset Follow-up visit, or if nonattendance telephone interview or mail, by study investigator	Interview with patients 1-10 d after rash onset by study investigators	Age, gender, severity of zoster rash (mild: covers <quarter of affected dermatome, severe: covers >3 quarters of affected dermatome, moderate: in between above), localisation of rash, prodromal pain, acute pain (none, mild, moderate, severe), antiviral use, analgesic use, allodynia (brush, stretch, and compression evoked), and pin-prick hypaesthesia	Logistic regression
Helgason et al.[21]	Iceland, 1990-1995	Patients presenting to participating GPs with first ever zoster diagnosis, without cognitive impairment; any age	421 recruited 391 analysed 30 lost to follow-up	Not available	PHN at 3 mo after zoster	28 (7.2)	Physician diagnosis and further confirmation by study investigators using clinical information from GPs and patients	Pain 3 mo after rash onset Telephone interview/home visit by principal investigator	Researcher interview, supplemented by data from GP practice records	Age and gender	Logistic regression
Jih, 2009[23]	Taiwan, 2000-2006	Patients with zoster in nationally representative 1 million claims data sample, with primary care and inpatient data linked; any age	34,280	Not reported (1->80)	PHN at 3 mo after zoster	Exact number not given (8.6)	*ICD-9* codes for zoster in inpatient or outpatient service claim	Pain >90 d after rash onset *ICD-9* zoster code and neuralgia treatment >90 d after first onset	*ICD-9* codes: timing of records with respect to zoster or PHN is unclear	Age, gender, diabetes, systemic lupus erythematosus, HIV/AIDs, breast cancer, liver cancer, and lymphoma/ leukaemia	Poisson regression
Jung et al.[25]	Europe, US, Canada, Australia, 1990-1991	Patients with immunocompetent zoster recruited into 2 clinical trials; aged ≥15 y	965 recruited 855 analysed 110 lost to follow-up	52.3 (range 15-93)*	PHN at 4 mo after zoster	114 (13.3)	Physician diagnosis of zoster within 72 h of rash onset	Pain 4 mo after rash onset Patient reported at follow-up visit	Physician interview at zoster diagnosis	Age, gender, rash severity, rash duration, prodrome, pain severity, primary involvement of the trigeminal dermatome, number of affected dermatomes, presence of affected nonadjacent dermatomes, clinical trial sample	Logistic regression

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Table 1 (*continued*)

Cohort studies

First author publication year	Country, year of study	Study population	Study size	Mean (SD) age in years at baseline	Outcome	Patients with PHN, n (%)	Definition and method of identifying zoster	Definition and method of ascertaining PHN	Method of ascertaining risk factor(s)	Risk factors assessed	Statistical analysis
Kanbayashi et al.[26]	Japan, 2008-2010	Patients treated at a hospital pain clinic, with zoster (unclear if acute/persistent); age unspecified	73 recruited all analysed	Median 69 (range 27-90)	Ordered categorical: no PHN, PHN 3-6 mo, PHN 6 mo+	PHN 3-6 mo: 13 (18) PHN 6 mo+: 25 (34)	Unclear	Pain 3-6 or 6 mo+ after rash onset Medical records of pain (unclear how pain defined)	Extraction of variables from clinical records at initial visit	Age, gender, comorbidities (hypertension, angina, diabetes, malignant tumour, autoimmune diseases) sleep disorder, rash location, period of onset, type and extent of pain, VAS, prodrome, allodynia	Ordered logistic regression
Katz et al.[27]	United States, mid 1990s	Patients presenting to hospital and community physicians with acute zoster; aged ≥18 y	129 recruited 102 analysed 8 lost to follow-up 19 excluded (initial assessment >30 d after rash onset)	Patients with PHN: 63.2 (15.1) Patients without PHN 59.2 (14.5)	PHN at 4 mo after zoster	20 (19.6)	Physician diagnosis with no more than 1 previous episode of zoster, +5 y ago	Pain ~4 mo after rash onset Telephone interview by research assistant or psychologist	Psychologist administered interview within 30 d of rash onset	Age, gender, race, education, marital status, physical health, immune compromise (definition unclear, yet includes HIV, currently treated for cancer and high-dose corticosteroids), presence of a prodrome, zoster location, zoster duration acute pain intensity, premorbid physical, role, and social functioning (1 wk before and after rash onset), symptoms of depression and anxiety, emotional well-being, personality disorder symptoms, health locus of control, disease conviction, hypochondriasis, somatosensory amplification, somatic symptoms, current major depression or dysthymia	Logistic regression

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Table 1 (*continued*)

Cohort studies

First author publication year	Country, year of study	Study population	Study size	Mean (SD) age in years at baseline	Outcome	Patients with PHN, n (%)	Definition and method of identifying zoster	Definition and method of ascertaining PHN	Method of ascertaining risk factor(s)	Risk factors assessed	Statistical analysis
Kotani et al.[28]	Japan, year not given	Patients presenting to hospitals with acute zoster, excluding patients recently on immunosuppressive therapy, or with serious neurologic disorders; aged ≥50	170 recruited all analysed	65 (9)	PHN at 2 mo after zoster	52 (30.4)	Physician diagnosis of painful nontrigeminal zoster (exc. disseminated) within 4 d of rash onset, and serological confirmation	Any pain 6 mo after rash onset Assessed 24 h after coming off analgesics, unclear how pain was ascertained	Measured at zoster diagnosis: method of ascertainment unclear	Age, gender, comorbid conditions (diabetes, malignancy, immune disorders, autoimmune disease), prodromal pain, localization, severity of zoster rash, number of skin lesions, degree of acute pain, cerebrospinal fluid interleukin 8 concentrations during and at healing of herpetic rash	Logistic regression
Opstelten et al.[33]	Netherlands, 1994-1999	Patients with zoster identified from EHRs from primary care; any age	837 identified all analysed	Not available	PHN at 3 mo after zoster	22 (2.6)	Medical code or zoster mentioned in the free text: confirmed after review of full medical records	Pain at 3 mo after rash onset Any evidence of pain in EHR; pain record/analgesic prescription	From previously recorded medical records at zoster diagnosis	Age, gender, localization, comorbidity (diabetes, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosus, psychological problem at zoster diagnosis), medication at zoster diagnosis (corticosteroids within previous 14 d and psycho-pharmaceuticals within previous 3 mo), painful prodrome, consultation frequency, chronic analgesics use	Logistic regression
Opstelten[35]	Netherlands, 2001-2004	Immunocompetent patients presenting to GPs with acute zoster and recruited into a trial; aged >50 y	598 recruited all analysed 651 not included: 470 refused consent, 98 physician declined to participate, 83 unknown†	66.2 (9.8)	PHN at 3 mo after zoster	46 (7.7)	Physician diagnosis within 7 d of rash onset, dermatome below C6	Pain ≥30 on VAS scale 3 mo after study inclusion. Patient filled in postal survey	Measured at baseline—questionnaire and data from GP	Age, gender, rash duration (in d) and severity, prodromal pain, pain severity, use of antivirals, VZV antibodies (IgM, IgA, IgG), VZV viremia, and seven psychological predictors: negative self-efficacy, pain catastrophizing, positive expectation, resignation, and trust in health care, anxiety state and anxiety disposition	Logistic regression

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Table 1 (*continued*)

Cohort studies											
First author publication year	**Country, year of study**	**Study population**	**Study size**	**Mean (SD) age in years at baseline**	**Outcome**	**Patients with PHN, n (%)**	**Definition and method of identifying zoster**	**Definition and method of ascertaining PHN**	**Method of ascertaining risk factor(s)**	**Risk factors assessed**	**Statistical analysis**
Park et al.[37]	South Korea, 2008-2010	Patients presenting to hospital with acute zoster; any age	55 recruited all analysed	PHN patients: 63.3 (15.9) Non-PHN: 48.2 (16.8)	PHN at 1 mo after zoster	15 (27.3)	Physician diagnosis within 7 d of rash onset	Pain persisting or appearing 30 d after rash onset Method unclear	Collected at baseline—method unclear	Age, sex, affected area, pain intensity, and interval between onset of rash and hospital visit. Also, maximal temperature difference between lesional and contralateral normal skin, and size of body surface area showing thermal asymmetry	Logistic regression
Parruti et al.[38]	Italy, 2006-2008	Consecutive patients presenting to primary care or hospital with acute zoster; age unspecified	469 recruited 441 analysed 28 lost to follow-up	58.1 (20.4)	PHN 1-3 mo after zoster	130 (29.5)	Physician diagnosis any time after rash onset, with laboratory investigation of uncertain cases	Any pain between 1-3 mo after enrolment Recorded at follow-up visit or by telephone	Patient completed electronic forms at enrolment	Age, gender, familial status, educational level, hypertension, diabetes, HCV and/or HIV infection, alcohol abuse smoking status, familial history of major cardiovascular events, malignancies, neurological diseases, major depression, psychiatric illness, allergy, trauma at site of lesion (in 6 mo pre-enrolment), surgical intervention at site of lesions, zoster dermatomeric district, pain intensity at presentation, rash severity, prescribed NSAIDs, antiviral use	Logistic regression
Volpi et al.[46]	Italy, 2001-2002	Patients with immunocompetent zoster presenting to private dermatologists, aged ≥18 y	533 recruited 219 analysed	Median age: 58 (18-82)	PHN 6 mo after zoster	70 (32)	Physician diagnosis	Pain 6 mo after rash onset, with pain rating 3 or higher (on scale from 0 [no pain] to 10) Physician diagnosis using patient reported pain at follow-up	Physician interview and patient completed questionnaire at zoster diagnosis	At baseline: age, gender, years of education, presence and duration of prodromal pain, intensity of pain, localization of rash, extent of rash, abnormal sensations (itch, tingle, allodynia), systemic antiviral therapy	Logistic regression

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Table 1 (*continued*)

Cohort studies

First author publication year	Country, year of study	Study population	Study size	Mean (SD) age in years at baseline	Outcome	Patients with PHN, n (%)	Definition and method of identifying zoster	Definition and method of ascertaining PHN	Method of ascertaining risk factor(s)	Risk factors assessed	Statistical analysis
Woznaik et al.[50]	United Kingdom, 1998-2001	Patients presenting to primary care with acute zoster; any age	280 recruited 104 analysed reasons for noninclusion not available	59 (range: 19-91)	PHN at 4 mo after zoster	70 (67.3)	Physician diagnosis plus confirmation by PCR for VZV	Pain/abnormal symptoms ≥120 d Follow-up visit or phone interview with study nurse	DNA preparation and APOE genotyping	APOE genotypes	ORs and 95% CI generated

Prospective case-base studies (where the controls are a sample of the base population)

First author publication year	Country year of study	Base population	Cases and controls	Study size	Mean age in years (SD)	Definition and method of identifying zoster	Definition and method of ascertaining PHN	Method of ascertaining risk factor(s)	Risk factors assessed	Statistical analysis
Choo et al.[8]	United States, 1990-1992	Acute zoster patients in HMO's EHRs, with continuous membership at least 180 d before and at least 90 d after zoster; age unspecified	Cases: patients developing PHN	37 cases	Cases: 67.6 (14.5)	*ICD-9* code for incident zoster (no zoster record before 6 mo). Medical records of all patients with a code screened by 2 reviewers	Symptoms in zoster area >60 d from rash onset	Screening of previously recorded medical records at the time of zoster diagnosis	Age, gender, health care utilization, location of zoster, prodromal symptoms, time to crusting of rash, interference of zoster with daily living, comorbidities recorded 180 d before zoster (diabetes, cancer, connective tissue disease, HIV, organ transplant), complications (superinfection, motor neuropathy, keratitis, uveitis, oticus, transient ischaemic attack, from vasculitis) cytotoxic chemotherapy 180 d before zoster, antiviral treatment, corticosteroids 180 d before and 30 d after zoster	Logistic regression with a correction

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Table 1 (*continued*)

Prospective case-base studies (where the controls are a sample of the base population)									
First author publication year	**Country year of study**	**Base population**	**Cases and controls**	**Study size**	**Mean age in years (SD)**	**Definition and method of identifying zoster**	**Definition and method of ascertaining PHN**	**Method of ascertaining risk factor(s)**	**Risk factors assessed**	**Statistical analysis**
			Controls: random sample of base population (PHN cases and noncases)	179 base population (controls sampled on a ratio of 3:1)	Controls 42.4 (17.5)		Patients with diagnoses, symptoms, meds indicating PHN screened by 2 reviewers			

* Excludes patients lost to follow-up. d, days; mo, months; SD, standard deviation.
† van Wijck AJ, Opstelten W, Moons KG, van Essen GA, Stolker RJ, Kalkman CJ, and Verheij TJ. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial. Lancet 2006;367:219–24.
APOE, alipoprotein E; C^, sixth cervical dermatome; DN4, neuropathic pain questionnaire with 4 questions; EQ-5D: questionnaire on zoster pain and health-related quality of life; EHR, electronic health care record; HADS, hospital anxiety and depression scale; HCV, hepatitis C virus; HMO, health maintenance organisation; *ICD-9*, International Classification of Diseases version 9; IFA, immunofluorescence of antigen; NPSI, neuropathic pain symptom inventory score; NSAIDS, Nonsteroidal antiinflammatory drugs; PCR, polymerase chain reaction; SF-12, short-form 12; VAS, visual analogue scale ranging from 0 (no pain) to 100 (worst pain ever experienced); VZV, varicella zoster virus; ZBPI, zoster brief pain inventory interference score.

years) (Appendix Table A2, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132). There was no evidence that the effect of age on PHN risk varied by definition of PHN ($P = 0.52$), ascertainment of PHN ($P = 0.14$), immunosuppression status ($P = 0.23$), or sources of study population ($P = 0.18$).

3.3.2. Gender

Of 9 studies reporting the age-adjusted association between gender and PHN, some suggested an increased risk of PHN among females,[9,25,38] others a decreased risk,[2,5] whereas others found no evidence of an association.[2,6,8,23,33,37] These conflicting results were supported by strong evidence of between-study heterogeneity ($P_{heterogeneity} < 0.001$; $I^2 = 73.9\%$). In posthoc analysis, the effect of female gender seemed protective in studies in which the mean age was ≥60 years, compared with among studies with mean age <60 years, for which female gender increased the risk of PHN; heterogeneity was reduced within these subgroups (<1% in both) (Appendix Table A2, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132). There was no evidence that the effect of gender on PHN risk varied by definition of PHN ($P = 0.45$), ascertainment of PHN ($P = 0.83$), immunosuppression status ($P = 0.25$), or sources of study population ($P = 0.97$). These analyses were limited by 4/7 studies in meta-analysis of gender having at least 1 bias domain assigned high-risk.

3.3.3. Severe immunosuppression

A cohort study among patients with zoster≥18 years found immunosuppression (including HIV, currently treated for cancer, or exposed to high-dose corticosteroids) was more common in patients with PHN (15%, n = 3/20) than without (7.3%, n = 6/82); but the sample size was too small to be conclusive.[27] Another cohort study among patients ≥50 years of age reintroduced 12 patients with immunosuppression excluded from the main analysis (defined as using high-dose oral corticosteroids/other immunosuppressive drugs, having invasive cancer or HIV/AIDS); these patients had an increased risk of PHN after adjustment for confounders (adjRR: 1.98, 95% CI: 1.14-3.45).[13] Finally, the case-base study in the United States found connective tissue disease, HIV, or organ allograft was associated with 10-fold increased risk of PHN, although the CI was wide (adjOR: 9.5, 95% CI: 2.0-45.0).[8] Two studies specifically assessed HIV: one excluded HIV from the final multivariable analyses,[38] whereas another found over 50% decreased risk of PHN among patients with HIV (antiretroviral treatment status not reported) (adjRR: 0.48, 95% CI: 0.26-0.86).[23] The latter study also reported strong evidence of an increased risk of PHN with lymphoma/leukaemia (adjRR: 1.74, 95% CI: 1.32-2.28).

3.3.4. Other physical comorbidities

3.3.4.1. Overall physical health

One study measured overall health status at zoster presentation using the physical component summary score and found a decreased risk of PHN with better physical health.[5] The second study summed total number of reported medical conditions and found no evidence of association with PHN.[27]

3.3.4.2. Autoimmune conditions

A large cohort study among 34,280 patients with zoster identified in Taiwanese electronic health insurance records identified 284 patients with systemic lupus erythematosus (0.83%), who were

Table 2

Association between PHN and various risk factors (defined as either vaccine-targetable or clinical features of the acute zoster episode): risk factors, adjusted effect measure and 95% confidence interval (CI) by study.

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	Severe immune suppression	Other physical or psychological comorbidities	Other risk factors	Pain (including prodrome)	Rash extent and location	Rash duration	Other
Cohort studies—risk factor: OR (95% CI) unless specified								
Asada et al.[2]	50 s: 1.20 (0.33-4.44) 60 s: 0.73 (0.19-2.79) 70 s: 1.72 (0.57-5.14) Reference ≥80 y F vs M: 0.48 (0.22-1.05)	—	—	Current smoker: OR not given History of zoster: 0.42 (0.09-1.88) Diameter of red skin after VZV skin test (≥5 vs <5 mm): 0.08 (0.02-0.45) Oedema after VZV skin test: 0.07 (0.01-0.62)	—	—	—	—
Bouhassira et al.[5]	≥70 vs <70 y 1.28 (1.05-1.55) F vs M 0.55 (0.34-0.90)	—	Physical health, using continuous PCS score, * per 1 unit increase (higher score = worse health): 0.72 (0.55-0.92) Mental Health, using continuous MCS score, * per one unit increase (higher score = worse health): $P = 0.59$ Associated disease (undefined), anxiety or depression not selected for final model	Family situation or living arrangements not selected for final model	Interference of pain on daily tasks, using continuous ZBPI score:1.18 (1.05-1.31) Neuropathic pain score at zoster presentation, using DN4 ≥4 vs <4: 1.78 (1.03-3.06) Intensity tactile allodynia, using continuous NPSI score: $P = 0.43$ Average pain intensity, using continuous score from 1-10 using ZBPI: $P = 0.54$ Pressure allodynia, brush-evoked allodynia not selected for final model	—	Delay in diagnosis not selected for final model	Analgesic treatment not selected for final model
Cebrián-Cuenca et al.†[6]	Per year increase: 1.04 (1.01-1.08, $P < 0.03$) Gender: OR not given $P > 0.05$	—	Other comorbidities (Unclear if in final model)	—	Prodromic pain (OR not reported: $P > 0.05$)	Zoster location (OR not reported: $P > 0.05$)	Time from symptom onset to diagnosis, time from appearance of eruption to diagnosis (OR not reported: $P > 0.05$)	Antiviral use: OR not given $P > 0.05$

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Table 2 (*continued*)

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	**Severe immune suppression**	**Other physical or psychological comorbidities**	**Other risk factors**	**Pain (including prodrome)**	**Rash extent and location**	**Rash duration**	**Other**
Coen et al.[9]	Age greater than 50 y: 3.91 (1.38-11.11) F vs M: 2.45 (0.96-6.23)	—	—	—	VAS >5: 3.92 (1.33-11.5) Prodrome not selected for final model	Extent of rash, score 1-5: 1 (least rash, baseline) 2: 1.01 (0.18-5.61) 3: 1.65 (0.31-8.80) 4: 1.08 (0.15-7.59) 5: 2.52 (0.45-14.0) Ophthalmic involvement: 3.20 (1.19-8.55)	Time from onset of rash (days): 0·93 (0.80-1.07)	—
Drolet et al.[12]	Per yr increase: RR: 1.02 (1.00-1.04) Gender not selected for final model	Immunosuppression (using high-dose oral corticosteroids or other immunosuppressive drugs, having invasive cancer or HIV/AIDS): RR: 1.98 (1.14-3.45) (sensitivity analysis)	Limitation in performing usual activities before zoster: RR: 1.66 (0.99-2.79) Having another pain condition or other pre-zoster EQ-5D measures not selected for final model	Income, baseline ≥50,000 USD: $40K-49,999: RR: 2.24 (0.98-5.13) $20K-39,999: RR: 1.77 (0.87-3.63) <$20K: 1.85 (0.89-3.83) Working status or education not selected for final model	Severe acute pain at zoster: RR: 2.06 (0.98-4.35) Prodrome and its duration reported, plus pain interference score not selected for final model	Number of lesions dermatome affected not selected for final model	Delay between recruitment and rash onset not selected for final model	Antiviral treatment, timing of antiviral treatment and other medications not selected for final model
Hannpaa et al.[19]	Per year increase: 1.06 (1.00-1.09) Gender: OR not reported (no association in univariate analysis)	—	—	—	Moderate/severe acute pain: OR not reported (no association in univariate analysis) Brush-evoked allodynia: 5.89 (1.50-23.1) Stretch-evoked allodynia: 4.13 (0.98-17.50) Compression-allodynia: OR not reported Prodrome not selected for final model	Severity and localization of rash: ORs not reported (neither associated in univariate analysis)	—	Pinprick hypesthesia: 7.72 (2.00-29.90) Antiviral use, analgesic use not selected for final model

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Table 2 (*continued*)

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	**Severe immune suppression**	**Other physical or psychological comorbidities**	**Other risk factors**	**Pain (including prodrome)**	**Rash extent and location**	**Rash duration**	**Other**
Helgason et al.[21]	Per 10 y increase: 2.11 (1.56-2.84) Gender not selected for final model	—	—	—	—	—	—	—
Jih et al.†[23]	≤60 vs >60 y: RR: 2.34 (2.17-2.53) F vs M: RR: 0.95 (0.89-1.03)	Lymphoma/leukaemia: RR: 1.74 (1.32-2.28) HIV/AIDs: RR: 0.48 (0.26-0.86)	Diabetes: RR: 1.35 (1.25-1.47) Breast cancer: RR0: 0.75 (0.53-1.06) Liver cancer: RR: 0.86 (0.65-1.15) SLE: RR: 2.27 (1.75-2.94)	—	—	—	—	—
Jung et al.[25]	Per year increase: 1.03 (1.01-1.05) F vs M: 2.01 (1.28-3.16)	—	—	—	Presence of a prodrome: 2.75 (1.18-6.38) Severe acute pain: 2.12 (1.35-3.32)	Severe rash: 3.00 (1.88-4.81) Primary involvement of the trigeminal dermatome, number of affected dermatomes, presence of affected nonadjacent dermatomes not selected for final model	Rash duration, continuous variable 0-24 h, 24-48 h, 48-72 h: 0.84 (0.64-1.11)	Clinical trial sample: 2.53 (1.61-3.99)
Kanbayashi et al.‡[26]	Per year increase in age group (<50, 51-74, ≥75): 2.74 (1.10-6.76) Gender not selected for final model	—	Diabetes: 3.08 (0.79-11.95) Sleep disorder: 1.16 (0.42-3.17) Hypertension, angina, autoimmune disorders, malignant tumour not selected for final model	—	Prodromal pain: 1.55 (0.55-4.41) Allodynia: 0.82 (0.24-2.81) Pain reduced by bathing: 3.39 (0.79-14.60) Deep pain: 4.24 (1.11-16.16) Breakthrough pain: 1.99 (0.62-6.42)	Localization not selected for final model	Period of onset (in days) not selected for final model	—

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Table 2 (*continued*)

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	**Severe immune suppression**	**Other physical or psychological comorbidities**	**Other risk factors**	**Pain (including prodrome)**	**Rash extent and location**	**Rash duration**	**Other**
Katz et al.[27]	Per y increase: 1.07 (1.01-1.12)	Immunosuppression (undefined, however, included HIV, currently being treated for cancer or high-dose corticosteroids): 1.59 (0.07-5.04)	Poorer physical health, continuous variable summing total number of medical conditions‡: 1.11 (0.93-1.32)	Race, education, marital status not selected for final model	Prodrome: 2.21 (0.54-9.15)	Localization not selected for final model	Zoster duration, per day: 0.97 (0.88-1.07)	—
	Gender not selected for final model		Personality disorder symptoms, per symptom increase: 1.09 (1.01-1.18)		Zoster interferes with role functioning: 2.34 (1.34-4.08)			
			Health locus of control, disease conviction, hypochondriasis, premorbid physical, role, and social functioning before zoster onset, depression, and anxiety symptoms not selected for final model		Acute pain intensity, 0-10 composite score§ continuous variable: 0.95 (0.69-1.32)			
					Somatosensory amplification and somatic symptoms not selected for final model			
Kotani et al.[28]	Per 10 y increase: 2.2 (1.1-4.5)	—	Diabetes, malignancy, or autoimmune disease not selected for final model	—	Prodrome: OR not reported	Localization not selected for final model	—	Cerebrospinal fluid interleukin 8 concentrations at healing of herpetic rash (per 20-μg/L increase: 1.8 (1.4-2.3)
	Gender not selected for final model				Acute pain: OR not reported	Severity of skin rash: OR not reported		
Opstelten et al.[33]	≤54: 1.00	—	Diabetes: 1.7 (0.5-6.2)	Consultation frequency not selected for final model	Painful prodrome: 1.2 (0.3-5.6)	Localization, ophthalmic vs not: 2.2 (0.8-6.5)	—	Chronic analgesics use not selected for final model
	55-74: 5.4 (1.1-26.5)		Psycho-pharmaceuticals uses 1.4 (0.·3-5.6)					

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Table 2 (*continued*)

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	**Severe immune suppression**	**Other physical or psychological comorbidities**	**Other risk factors**	**Pain (including prodrome)**	**Rash extent and location**	**Rash duration**	**Other**
	≥75: 19.7 (4.3-90.9)		Chronic obstructive pulmonary disease, rheumatoid arthritis, SLE, psychological problem or corticosteroid use at zoster diagnosis not selected for final model					
	F vs M: 1.0 (0.9-1.0)							
Opstelten[35]	Per y: 1.08 (1.04-1.12)	—	Trust in health care score, 1 unit increase from 0-100 (higher score relates to lower trust): 1.01 (1.00-1.03)	—	Severity of acute pain, per VAS unit: 1.02 (1.01-1.03)	Severe rash, ≥43 vesicles: 2.31 (1.16-4.58)	Duration of rash before consultation, in days: 0.78 (0.64-0.97)	Use of antivirals, VZV antibodies (IgM, IgA, IgG), VZV viremia not selected for final model
	Gender not selected for final model		Psychological predictors including anxiety disposition not selected for final model					
Park et al.[37]	≥60 vs <60 y: 8.50 (1.17-61.60)	—	—	—	VAS for pain, ≥5 vs <5: 4.78 (0.78-29.33)	Localization not selected for final model	Onset of rash, >3 d vs ≤3 d: 0.53 (0.08-3.28)	Temperature differences between normal and affected skin: <0.5°C (baseline) 0.5°C-1.0°C: 8.25 (1.06-64.40) >1.0°C: 30.26 (1.68-544.06) % body surface area with thermal asymmetry^2, ≥3 vs <3%: 8.25 (0.24-12.38)
	F vs M: 0.73 (0.13-4.24)							
Parruti et al.[38]	Per 10 y increase: 1.01 (0.99-1.02)	HIV not selected for final model	Trauma at site of lesion:2.53 (1.37-4.65)	Current/former smoking: 2.08 (1.22-3.55)	Intense/very intense pain at presentation: 2.19 (1.32-3.65)	Site of lesions and severity of rash not selected for final model	—	Antiviral use and NSAIDs not selected for final model
	F vs M: 1.39 (0.84-2.30)		Surgical intervention at site of lesion: 1.33 (0.79-2.25)	Alcohol abuse, familial status, educational level not selected for final model				

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Table 2 (*continued*)

	Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
	Age and gender	**Severe immune suppression**	**Other physical or psychological comorbidities**	**Other risk factors**	**Pain (including prodrome)**	**Rash extent and location**	**Rash duration**	**Other**
			HCV infection, hypertension, diabetes, neoplasm, neurological disorders, psychiatric illness, allergy, or family history of major cardiovascular events, malignancies, neurological diseases, major depression not selected for final model					
Volpi et al.[46]	>50 y vs ≤50: 2.58 (1.33-4.98) Gender not selected for final model	—	—	Years of education not selected for final model	Duration of prodromal pain (≤3 vs >3 d): 0.49 (0.24-0.99) Intensity of pain using the Short Italian questionnaire, from 0-10 continuous variable: 1.17 (1.02-1.34) Presence of prodromal pain not selected for final model	Extent of rash: (>1 vs 1 dermatome): 2.27 (1.16-4.55) Localization of rash not selected for final model	—	Antiviral therapy: 0.51 (0.10-2.50) Abnormal sensations: 1.11 (1.02-1.34)
Wozniak et al.[50]	—	—	—	APOE-ε3: 4.98 (1·88-13.23) APOE-ε4:0.25 (0.09-0.7) (females only—no effect among males)		—	—	—
Case-base studies—risk factor: prevalence ratio (95% CI)								
Choo et al.‖[8]	Per y: 1.12 (1.06-1.18) F vs M: 0.9 (0·4-2.3)	Connective tissue disease, HIV infection or organ allograft: 9.5 (2.0-45.9)	Diabetes: 2.7 (0.4-17.·9) Cancer: 0.1 (0.02-0.9)	Number of encounters previous 180 d: 0-2 (reference) 3-4: 0.3 (0.1-0.9)	Prodromal symptoms: 3.4 (1.3-9.1) Interference of pain on activities on daily living: 1.3 (0.4-4.2)	Thoracic (reference), Cranial nerve V: 1.7 (0.3-9.3), Cervical: 1.1 (0.3-4.5), Lumbar/sacral: 0.6 (0.2-2.0) Complications (baseline is none): Superinfection: 1.9 (0.5-7.6), Ocular: 2.1 (0.7-6.3), Oticus/TIA from vasculitis/motor neuropathy: 0.6 (0.2-2.0)	—	Acyclovir exposure after rash onset, days (baseline is no exposure): 0-3: 1.0 (0.4-2.6) 4-30: 1.0 (0.3-4.0)

(*continued on next page*)

Table 2 (*continued*)

Vaccine-targetable risk factors				Clinical features of the acute zoster episode			
Age and gender	Severe immune suppression	Other physical or psychological comorbidities	Other risk factors	Pain (including prodrome)	Rash extent and location	Rash duration	Other
		Corticosteroid exposure before zoster: 1.4 (0.3-6.0)	5-7: 0.4 (0.1-1.4) >7:0.9 (0.4-2.3)				Corticosteroid exposure after zoster, 0-30 d vs none: 0.7 (0.2-2.6) Cytotoxic chemotherapy 180 d pre-zoster not selected for final model

Please note; reference category listed last.
All risk factors included in the final multivariable model are listed, unless otherwise specified.
*Adjusted for age and gender only.
†Thermal asymmetry index measures impairment of thermal sensation of affected vs unaffected side, vibratory asymmetry index measures impairment of vibration perception of affected vs unaffected side.
‡ Physical Health measured using the Life Stressors and Social Resources Inventory, which sums the total number of patient reported medical conditions.
§composite score ranges from 0-100 numerical pain ratings and McGill Pain Questionaire Present Pain Intensity ratings of average and worst shingles pain.
‖ Adjusted for age (continuous variable), presence (yes or no) of prodromal symptoms, severe pain, or comorbid conditions; and number of health care encounters.
APOE, alipoprotein E; DN4, Neuropathic pain questionnaire with 4 questions; EQ-5D, questionnaire on zoster pain and health-related quality of life; HCV, Hepatitis C virus; NPSI, neuropathic pain symptom inventory score; RR, rate ratio; SF-12, short-form 12; SLE, systemic lupus erythematosus; VAS, visual analogue scale, ranging from 0 (nonpain) to 100 (worst pain ever experienced); VZV, varicella zoster virus; y, year; ZBPI, zoster brief pain inventory interference score.
¶ PCS, physical component summary score, MCS, mental component summary score (a patient reported survey of physical/mental health using short form 12 (SF-12): score <50 represented below-average health status).
#Study used ordered logistic regression, therefore the parameters represent the exposure ORs for being the highest outcome categories, compared with the lowest outcome categories: it is assumed the effect of exposure is the same for all splits of the outcome categories.

more than twice as likely to develop PHN (adjRR: 2.27, 95% CI: 1.75-2.94).[23] Another smaller study (N = 837) using electronic medical records from the Netherlands collected data on lupus and rheumatoid arthritis; however, they were not included in the final model (numbers not reported).[33]

3.3.4.3. Diabetes

Three cohort studies reported point estimates for the association between diabetes and PHN ≥1 in multivariable analyses; however, there was insufficient evidence to confirm an association.[8,26,33] A larger cohort study among 34,280 patients with zoster did find evidence of an increased risk (adjRR: 1.35, 95% CI: 1.25-1.47).[23] There was no evidence of between-study heterogeneity for studies reporting age-adjusted diabetes effects ($P_{heterogeneity}$ = 0.564; I^2 = 0.0%); the pooled effect estimate was 1.36 (95% CI: 1.25-1.47) in the fixed effect meta-analysis; however, the large study (N = 34,280) dominated the pooled relative risk (contributing 99.1% to the model).

3.3.4.4. Cancer

Five studies investigated cancer and its relationship with PHN; 3 excluded it from the final model.[26,28,38] Breast and liver cancer were investigated in a single study, but were not associated with PHN in the final adjusted model.[23] The case-base study found 13.5% of PHN cases and 4.7% of non-PHN controls had a cancer diagnosis 180 days before zoster[8]; after adjustment, cancer was associated with a reduced risk of PHN (adjOR: 0.1, 95% CI: 0.02-0.9); however, the CIs were wide. A meta-analysis for cancer effect estimates was not conducted as they involved different cancer sites.

3.3.4.5. Recent physical trauma

The only study to investigate this risk factor reported over 2-fold increased risk of PHN associated with experiencing trauma at the zoster site (contusions, burnings, wounds, and multiple traumas) within 6 months before study enrolment.[38]

3.3.4.6. Other

Other physical conditions investigated as predictors of PHN, but not included in the age-adjusted models included surgical intervention,[38] hepatitis-C virus infection,[38] hypertension,[26,38] neurological disorders,[38] allergy,[38] family history of coronary heart disease,[38] angina,[26] and chronic obstructive pulmonary disorder.[33]

3.3.5. Psychological comorbidities

These were assessed as risk factors for PHN in 4 studies. Two cohort studies assessed a range of psychological comorbidities; only personality disorder symptoms (adjOR: 1.09, 95% CI: 1.01-1.18),[27] and lower levels of trust in health care (adjOR: 1.01, 95% CI: 1.00-1.03)[35] showed a small association with PHN in multivariable analyses. Neither depression nor anxiety was included in multivariable analyses.[5,27,35,38]

3.3.6. Other risk factors

A cohort study found alipoprotein E-ε3 was more common and alipoprotein E-ε4 less common among female patients with zoster and PHN, suggesting that this host genetic factor may influence the risk of PHN.[50] One study found evidence that current/former smoking was associated with greater risk of PHN (adjOR: 2.08, 95% CI: 1.22-3.55)[38] whereas another included it in their final model, but did not report the association.[2] One study suggested a low state of varicella zoster virus (VZV)-specific

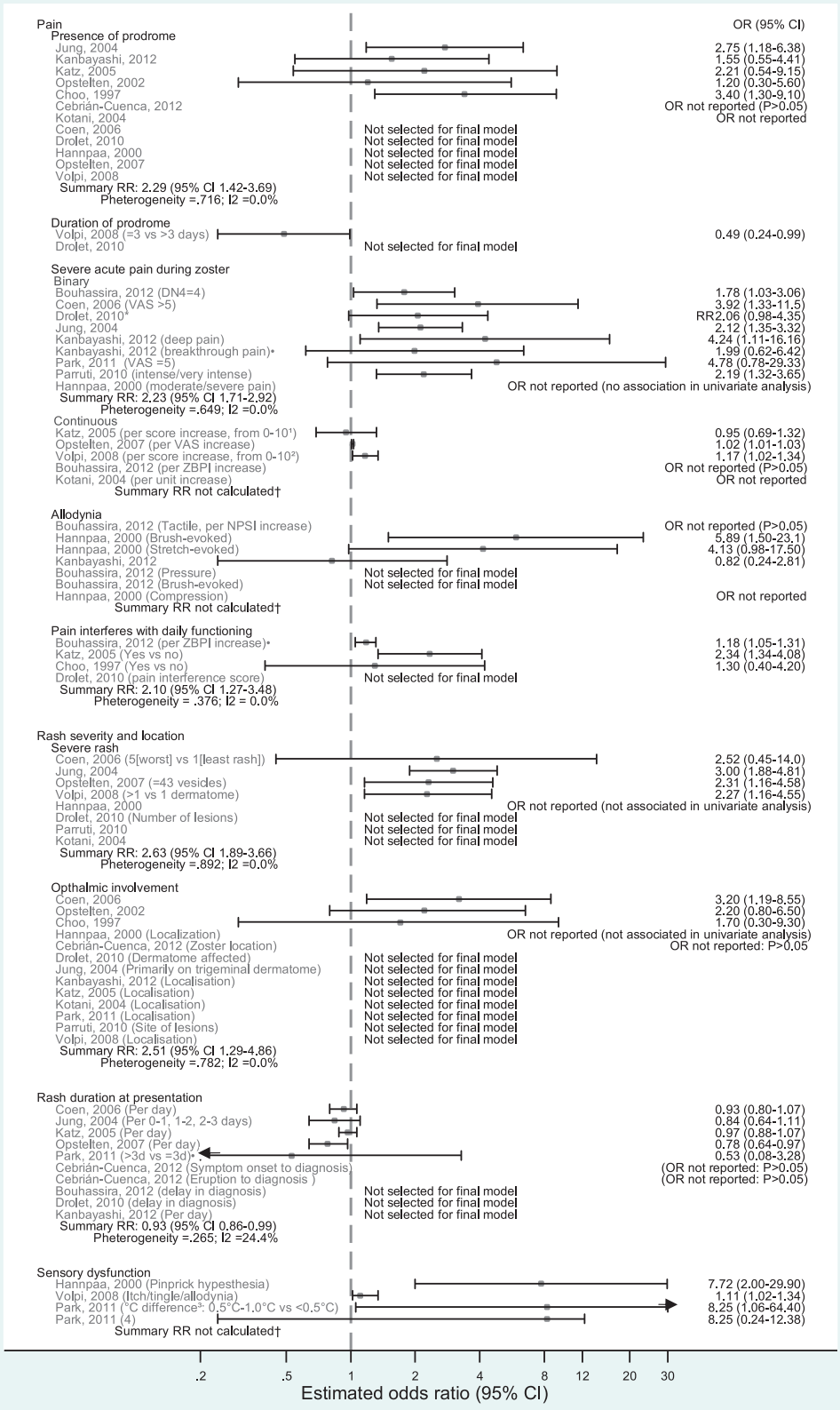

Figure 2. Summary of associations between postherpetic neuralgia and clinical features of acute zoster. [1]Composite score ranges from 0-100 numerical pain ratings and McGill Pain Questionnaire Present Pain [2]Intensity ratings of average and worst shingles pain. Intensity of pain using the Short Italian questionnaire, from 0-10. [3]Temperature differences are between normal and affected skin. [4]Percentage of body surface area thermal asymmetry (≥3 vs <3%). †Risk factors too varied to combine in meta-analyses. •Not included in summary RR (either because study has already contributed to meta-analysis, or exposure definition is not in-keeping with other studies). *Studies reporting RR (rather than OR) are not included in meta-analysis. CI, confidence interval; DN4, Neuropathic pain questionnaire with 4 questions; NPSI, Neuropathic pain symptom inventory score; OR, odds ratio; RR, rate ratio; SF-12, short-form 12; VAS, visual analogue scale ranging from 0 (non pain) to 100 (worst pain ever experienced); VZV, varicella zoster virus; ZBPI, Zoster brief pain inventory interference score.

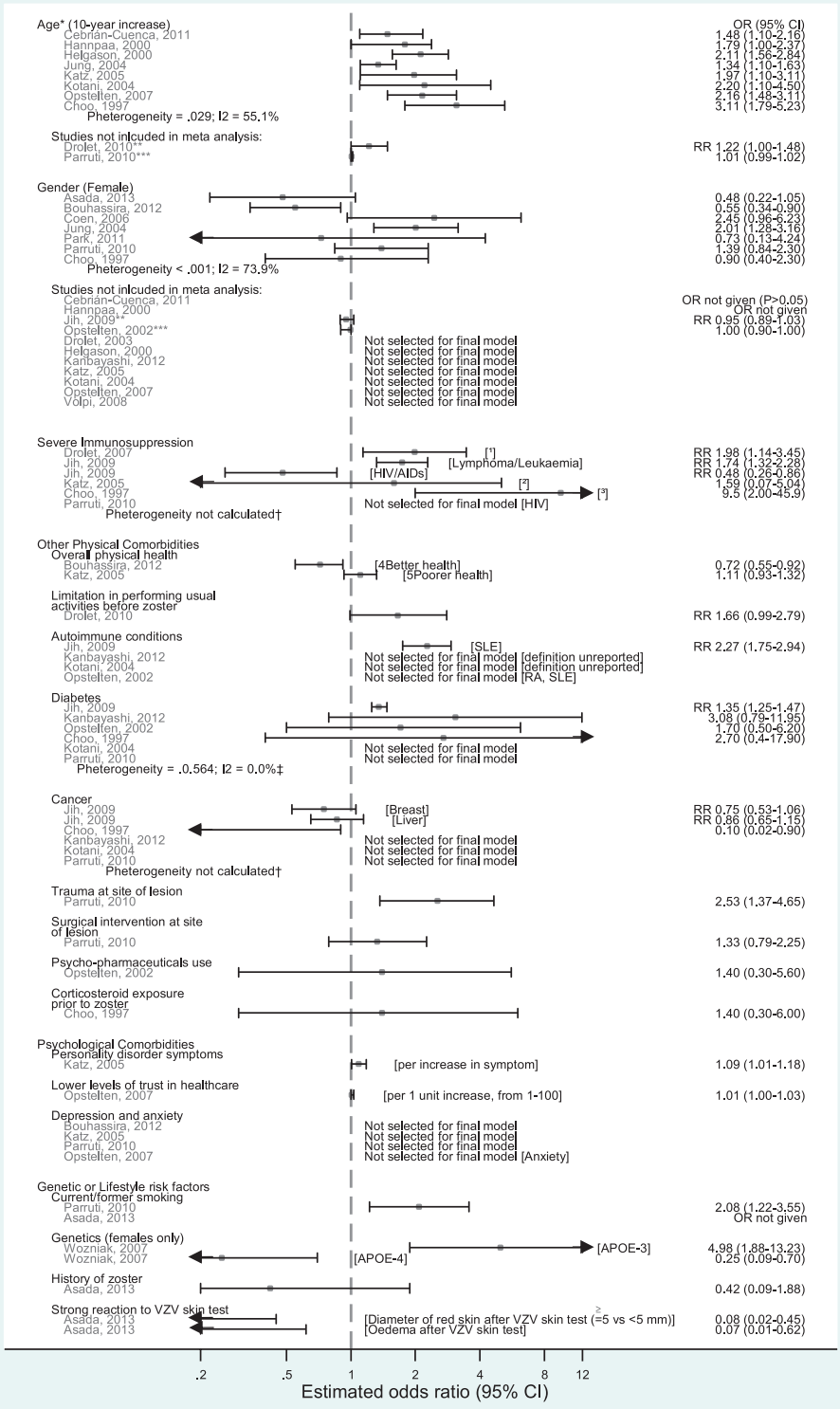

Figure 3. Summary of associations between postherpetic neuralgia and vaccine-targetable risk factors from identified studies. *Only 10/20 studies reported age such that the effect estimate could be converted into 10-year increases. Of the remaining 10 studies; 8 reported an increased risk of PHN with greater age, 1 showed no effect all, and 1 did not report an age-effect. **Studies reporting RRs rather than ORs not included in meta-analysis as RR can underestimate OR when outcome becomes common. ***Effect estimate from study may be erroneous therefore the study is not included in the meta-analysis: Parruti 2010 CIs are too narrow, and Opstelten 2002 confidence also too narrow. [1]Using high-dose oral corticosteroids or other immunosuppressive drugs, having invasive cancer or HIV/AIDS. [2]Undefined, however included HIV or currently being treated for cancer. [3]Connective tissue disease, HIV infection or organ allograft. [4]Better health: measured using continuous physical component summary score (higher scorer score reflects worse health). [5]Poorer health: measured using continuous variable of total number of medical conditions. †Risk factors too varied to combine in meta-analyses. ‡The large study by Jih et al. (N = 34,280) dominated the pooled relative risk contributing to 99·1% of the model. Other risk factors investigated as predictors of PHN, but not included in the final model, included; surgical intervention, hepatitis-C virus infection, hypertension, neurological disorders, allergy, family history of CHD, angina, chronic obstructive pulmonary disorder, education, alcohol abuse, familial status, years of education and race. APOE, alipoprotien E; CI, confidence interval; OR, odds ratio; RA, rheumatoid arthritis; RR, rate ratio; SLE, systemic lupus erythematosus.

Table 3

Assessment of bias for individual studies (◆= High risk, ■= Medium risk, O=Low /no risk or ?=Unclear risk).

Type of bias	Confounding	Selection bias	Exposure information bias	Outcome (PHN) information bias		Bias due to missing data
	Residual confounding by age	Loss to follow-up	Nondifferential misclassification	Reporting bias	Nondifferential misclassification	Missing exposure data
Asada et al.[2]	O	O	O	O	?	◆
Bouhassira et al.[5]	◆	■	O	O	?	?
Cebrián-Cuenca et al.[6]	O	■	O	O	?	O
Coen et al.[9]	◆	O	?	O	?	?
Drolet et al.[12]	O	O	O	O	?	■
Haanpaa et al.[19]	O	■	O	■	?	?
Helgason et al.[21]	O	O	O	O	?	O
Jih et al.[23]	◆	?	?	◆	◆	?
Jung et al.[25]	O	■	O	O	?	O
Kanbayashi et al.[26]	◆	O	◆	?	◆	O
Katz et al.[27]	O	O	■	■	?	O
Kotani et al.[28]	O	O	?	?	?	?
Opstelten et al.[33]	◆	O	O	◆	◆	■
Opstelten[35]	O	O	O	O	?	■
Park et al.[37]	◆	O	?	?	?	?
Parruti et al.[38]	O	O	O	O	?	■
Volpi et al.[46]	◆	◆	O	O	?	■
Wozniak et al.[50]	O	?	O	?	?	O
Choo, 1997[8]	O	O	O	■	■	■

PHN, Postherpetic neuralgia.

cell-mediated immunity, evidenced from reduced response to VZV skin-test, was associated with greater risk of PHN.[2] Studies investigating education,[13,27,38,46] race,[27] being married,[5,27,38] being in work,[13] consultation rate,[8,33] or alcohol abuse[38] did not select these risk factors in their final model.

Nine of the 19 studies had 2 or more definitions of PHN. Briefly, studies additionally defined PHN as pain at 1[6,8,13,21,33,35,38] (n = 7) and 6 months[9,21,28] (n = 3) after zoster onset; there were no major differences in study findings using these alternative definitions, except older age was a stronger risk factor for pain persisting 6 months, compared with 2 or 3 months, after zoster (Appendix Table A3, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132), indicating older age may be a risk factor for long-term PHN.

3.4. Assessment of bias

Our assessment of bias found 8/19 studies with at least 1 prespecified domain with a high risk of bias, 8 studies with at least 1 domain of medium risk, and 3 studies with only low or unclear risk of bias. Residual confounding by age was the most common source of potential bias, affecting 7/19 studies requiring age-adjustment (**Table 3**). Studies using electronic health care records were at greatest risk of reporting bias; specifically ascertainment bias, where outcome ascertainment relies on patients returning to their GP and higher general practice (GP) attendance could have increased the chance of PHN diagnosis.[8,23,26,33] Of the cohort studies, 5 experienced loss to follow-up of greater than 10% (**Table 3**). See Appendix Table A4 for detailed note on the bias assessment (available online as Supplemental Digital Content at http://links.lww.com/PAIN/A132).

The funnel plot gave a relatively symmetric pattern, suggesting that there was little indication of publication bias (**Fig. 4**). The distribution did not suggest that more extreme findings were being selectively published.

The sampling methods and patient characteristics of some studies suggest their external validity may be limited; characteristics of included patients indicate a nonrepresentative sample in some studies (Coen et al. reported that 20% of the study population was immunosuppressed[8] and in 3 studies over 30% of the cohort developed PHN[28,46,50]); 1 study used convenience sampling,[6] thus not all population members had an equal probability of being selected; and the number or characteristics of eligible patients refusing to participate were unclear in most studies.

4. Discussion

4.1. Summary of evidence

Our systematic review identified 19 prospective studies investigating risk factors for PHN. There was good evidence that clinical features of acute zoster including prodromal pain, severe

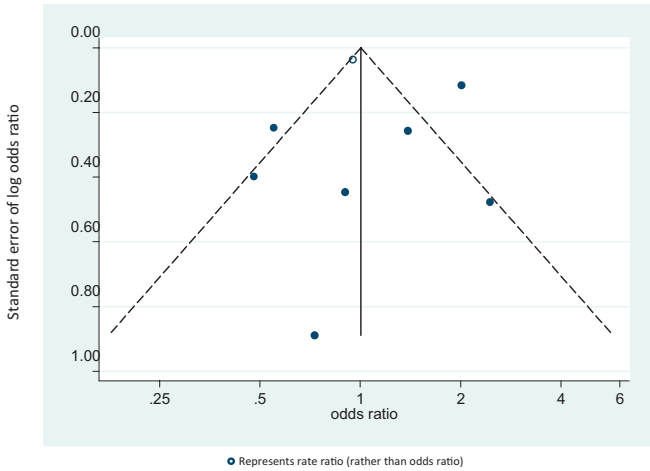

Figure 4. Assessment of publication bias for gender as a risk factor for postherpetic neuralgia. Funnel plot of the log odds ratio plotted against the standard error of the log odds ratio for seven studies reporting the effect of female gender on PHN risk (dotted line represents pseudo 95% confidence limits).

acute pain, severe rash, and ophthalmic involvement were associated with increased risk of PHN. Rash duration at zoster presentation was less strongly associated with PHN. Regarding vaccine-targetable risk factors, older age was consistently associated with PHN. The evidence for gender as a risk factor was conflicting. Immunosuppression and diabetes were significantly associated with PHN in a few, but not all studies. Systemic lupus erythematosus, recent trauma, and personality disorder symptoms were associated with PHN; however, evidence came from single studies only. No studies found evidence suggesting that depression or cancer was associated with increased risk of PHN. Most studies had small sample sizes reducing their power to detect associations. Our review highlights that we have a good understanding of which clinical features of zoster predict PHN, yet there is a need for better evidence on common and potentially easily vaccine-targetable risk factors for PHN prevention.

4.2. Interpreting the findings

It is believed that several pathophysiological mechanisms may contribute to the development of PHN. Acute zoster infection undoubtedly results in nerve damage to both the peripheral and central nervous system, yet the nature of the damage and specific mechanism resulting in persistent pain are not fully understood.[4] There are 2 (nonmutually exclusive) hypotheses for its development; the first is that persistence of VZV after acute zoster, at higher levels than during latency, causes continued pain; and the second, that after acute zoster infection, there is increased neuronal excitability and alteration of pain perception caused by neural damage.[1,20]

The variety of possible risk factors for PHN identified in the review may reflect these different mechanisms.[3] The finding that greater rash severity and greater acute pain are associated with increased risk of PHN supports the notion that greater neural damage caused by more severe infection contributes to the development of PHN.[15] That longer rash duration was associated with reduced risk of PHN initially seems inconsistent with the finding that more severe zoster rash is associated with PHN. However, late presentation might indicate patients had milder zoster not immediately demanding medical attention. Either way, this finding is unlikely to be due to the duration of the rash itself. Patients with ophthalmic zoster seem at greater risk of PHN, although it is not clear whether concerns about eye complications cause them to react differently, rather than the increased risk being driven by a biological mechanism.[20] Ageing undoubtedly causes a waning of cell-mediated immunity and may cause increased levels of the virus after zoster reactivation, potentially causing PHN. Other risk factors for PHN identified here are also associated with reduced cell-mediated immunity, including severe immunosuppression, systemic lupus erythematosus, and smoking. Trauma at the site of the rash may induce local changes facilitating reactivation of herpes zoster (HZ) and greater nerve damage leading to increased risk of PHN. However, the aetiological mechanism(s) by which these risk factors affect the development of PHN remains largely unknown.

4.3. Limitations of the selected studies

The included studies had some limitations. Many had small sample sizes, and we were unable to combine some results in a meta-analysis. Furthermore, many tested a number of risk factors; the associations observed may occur by chance due to testing multiple exposures. Most studies based zoster diagnosis on clinical opinion rather than serological or virological testing; this may have led to misclassification of patients with zoster; however, clinical diagnosis is typically reliable.[34]

Some studies may have been affected by specific biases. Age is a very strong predictor of PHN and yet 7/18 studies assessing age adjusted for it as a binary or categorical variable with wide age intervals, potentially causing residual confounding by age. Loss to follow-up affected 5/19 studies, and if loss to follow-up is associated with both PHN and the risk factor, bias could have been introduced.[18] Patients with PHN may be more likely to return for follow-up as they require continued care, and patients with particular risk factors may also return to their GP more commonly, making bias due to loss to follow-up likely. Ascertainment bias may have affected studies using routinely collected health care data. Here, spurious associations between PHN and medical conditions requiring regular contact with health care professionals may arise. One such study adjusted for health care utilisation[8] and still found a positive association with PHN and certain immunosuppressive disorders, suggesting the effect cannot be driven solely by ascertainment bias. Finally, not all studies adjusted for clinical features of the acute zoster episode,[2,21,23] and results may be subject to residual confounding.

4.4. Strengths and limitations of the review

This is the first study to systematically review the literature on risk factors for PHN; although clinical features of acute zoster have been acknowledged as risk factors for PHN, this is the first to summarise age-adjusted results and pool them in a meta-analysis. We undertook a comprehensive search of several databases using multiple keywords and indexed subject headings. The reliability of study selection criteria was confirmed by double screening of 10% of the articles.

There are some important limitations to this review. There is no consensus over the exact definition of PHN; in this review, PHN definitions ranged from pain persisting 1 to 6 months after rash onset, with some studies assessing *any* pain, whereas others required severe pain. A full assessment of risk factors by different PHN classifications was not possible here because of too few studies.

Between-study variability prevented us from pooling the effects of age and gender on PHN; there was some evidence that age of the study population contributed to the observed heterogeneity. However, these analyses were limited by the small number of studies and may have reduced our power to detect associations. Variability may be due to different adjustment for confounders or some studies reporting biased effect estimates, eg, due to PHN measurement error or loss to follow-up. Studies also used different definitions for certain clinical features of acute zoster, such as severe acute pain and severe rash, potentially giving some heterogeneity to the results.

Our search strategy may have missed some studies; however, we used multiple databases (including grey literature) and searched reference lists of selected articles, to minimise this issue. As with any literature review, studies finding no effects may have gone unpublished. Our funnel plot did not demonstrate any evidence of publication bias with respect to assessing gender as a risk factor for PHN. However, publication bias may affect other risk factors differently, and there were not enough studies per risk factor to assess this for other exposures. Finally, non–English-language articles were excluded because of resource limitations; however, the authors believe it is unlikely to have led to the omission of any major articles in the area.

4.5. Implications

Zoster vaccination offers a way of preventing this debilitating complication by preventing zoster itself, but is currently

expensive; therefore, targeting the vaccine toward groups at high-risk of PHN may be beneficial. The vaccine is currently licensed in certain countries in the European Union, United States, and Australia.[49] It is targeted at older age groups and contraindicated in patients with severe immunosuppression. As older age is the only indisputable risk factor that vaccination policies can use, this approach seems reasonable. If patients with severe immunosuppression are at increased risk of PHN as suggested by this review, in addition to being at greater risk of zoster itself, there is even more need to identify alternative strategies to prevent zoster in these groups.

This review has highlighted our lack of understanding of vaccine-targetable risk factors for PHN, and the need to perform studies exploring suggested associations. Such studies would need to be generalizable to a wide group, by recruiting patients aged 18 and over and including immunosuppressed patients, to examine the risk of PHN by age and immunosuppression status. Other desirable features would include recruiting a large number of individuals to achieve greater power to help detect small effects, collecting data on all known and possible risk factors for PHN, actively following up patients with zoster to allow persistent pain to be identified for the entire cohort at the same time and reducing loss to follow-up to avoid differential ascertainment of PHN. Finally, at the analysis stage, detailed adjustment for age using either a continuous or finely categorised age variable would reduce residual confounding by age.

5. Conclusions

This study confirms that features of the acute zoster episode, including prodromal pain, severe rash, severe acute pain, and ophthalmic involvement are risk factors for PHN. Our current understanding of vaccine-targetable risk factors for PHN is however limited. There are some suggestions that immunosuppression, systemic lupus erythematosus, diabetes, and recent trauma may be associated with greater risk of PHN. Increasing age is the only established risk factor for PHN that has been quantified with sufficient rigour as to usefully inform vaccine policy. Larger studies with greater power to detect associations, and studies addressing the limitations of previous research, may elucidate some of the unknown risk factors for PHN.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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The funding source had no role in the study design; data collection, analysis, or interpretation of the data or writing of the report. H. J. Forbes has access to all studies identified from the initial search. The corresponding author has full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A132.

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