**Appendix**

**Data extraction details**

**Risk of bias assessment details**

**Letters to authors**

**Table A1:** Table of 97 studies excluded after full-text review

**Table A2:** Sub group meta-analyses to identify causes of heterogeneity for effect of age and gender on PHN.

**Table A3:** Associationbetween PHN and various risk factors: risk factors, adjusted effect measure and 95% confidence interval by study.

**Table A4:** Assessment of bias: detailed notes

**Data extraction details**

The following data were extracted for the selected studies by HF; study characteristics including, study design, country and year(s) of study, study size, study population (including mean age and range), definition and method of ascertaining zoster cases, risk factors assessed and how they were ascertained, definition and method of ascertaining PHN, % with PHN, and statistical analysis. We extracted all study results from the final age-adjusted model, including the multivariable effect estimates when available (e.g. adjusted relative risks (RR), or odds ratios (OR) with 95% confidence intervals (CI)) and any other relevant analysis (such as sub-group analysis or investigation of effect modification).

**Risk of bias assessment details**

The risk of bias was assessed separately for each study using the following pre-specified domains; residual confounding by age, selection bias, exposure and outcome information bias and bias due to missing data. We formulated our assessment based on the Cochrane Collaborations approach, where domains are categorised as having; “High risk” (bias may alter the results seriously), “Medium risk” (bias may alter the results moderately), “Low/No risk” (bias, if present, is unlikely to alter the results seriously) or “Unclear risk” (a risk of bias that raises some doubt about the results). Support for each judgement of risk is provided in the appendix (Table A3).

**Letter to authors**

Dear *[author name]*

I am carrying out a systematic review of studies investigating risk factors for postherpetic neuralgia (PHN). This is part of my PhD on zoster epidemiology, and we also aim to publish the review as a paper. I have identified the studies to be included in the review, one of which is the following study in which you are listed as corresponding author:

[*Reference*]

I am now extracting data from study reports to summarise in the review. I would be most grateful if you could clarify a few points (listed below) regarding your methods and results?

*[Specific questions]*

Your help would be greatly appreciated as I am keen to summarise your study as accurately and completely as possible.

Many thanks

Harriet

**Table A1: Table of 97 studies excluded after full-text review.**

| **Reason for exclusion** | **Author** | **Year** | **Title** | **Journal** |
| --- | --- | --- | --- | --- |
| **PHN patients compared to non-zoster controls** | G. H. G. Ashrafi, E.:Montague, P.:Forster, T.:Ross, A.:Ghazal, P.:Scott, F.:Breuer, J.:Goodwin, R.:Kennedy, P. G. E. | 2010 | Assessment of transcriptomal analysis of varicella-zoster-virus gene expression in patients with and without post-herpetic neuralgia | Virus Genes |
| T. M. F. Battcock, R.:Barnes, R. M. R. | 1990 | Observations on herpes zoster: 1. Residual scarring and post-herpetic neuralgia; 2. Handedness and the risk of infection | British Journal of Clinical Practice |
| D. Bosco, M. Plastino, M. De Bartolo, D. Cristiano, M. Ettore, G. Zurlo, F. Bosco, C. Colica, F. Tallarigo and A. Fava | 2013 | Role of impaired glucose metabolism in the postherpetic neuralgia | Clinical Journal of Pain |
| J. Y. Chen, C. Y. Chang, P. H. Feng, C. C. Chu, E. C. So and M. L. Hu | 2009 | Plasma vitamin C is lower in postherpetic neuralgia patients and administration of vitamin C reduces spontaneous pain but not brush-evoked pain | The Clinical journal of pain |
| J. Y. Chen, C. C. Chu, Y. S. Lin, E. C. So, J. P. Shieh and M. L. Hu | 2011 | Nutrient deficiencies as a risk factor in Taiwanese patients with postherpetic neuralgia | British Journal of Nutrition |
| M. R. Clark, L. J. Heinberg, J. A. Haythornthwaite, A. L. Quatrano-Piacentini, M. Pappagallo and S. N. Raja | 2000 | Psychiatric symptoms and distress differ between patients with postherpetic neuralgia and peripheral vestibular disease | Journal of Psychosomatic Research |
| M. E. G. Devlin, D. H.:Mahalingam, R.:Dueland, A. N.:Cohrs, R. | 1992 | Peripheral blood mononuclear cells of the elderly contain varicella-zoster virus DNA | Journal of Infectious Diseases |
| A. Gatti, F. Pica, M. T. Y. Boccia, F. De Antoni, A. F. Sabato and A. Volpi | 2010 | No evidence of family history as a risk factor for herpes zoster in patients with post-herpetic neuralgia | Journal of Medical Virology |
| A. Ozawa, Y. Sasao, K. Iwashita, M. Miyahara, J. Sugai, M. Iizuka, Y. Kawakubo, M. Ohkido, T. Naruse, T. Anzai, N. Takashige, A. Ando and H. Inoko | 1999 | HLA-A33 and -B44 and susceptibility to postherpetic neuralgia (PHN) | Tissue Antigens |
| M. Sato, J. Ohashi, N. Tsuchiya, K. Kashiwase, Y. Ishikawa, H. Arita, K. Hanaoka, K. Tokunaga and T. Yabe | 2002 | Association of HLA-A\*3303-B\*4403-DRB1\*1302 haplotype, but not of TNFA promoter and NKp30 polymorphism, with postherpetic neuralgia (PHN) in the Japanese population | Genes and Immunity |
| D. Weitzman, O. Shavit, M. Stein, R. Cohen, G. Chodick and V. Shalev | 2013 | A population based study of the epidemiology of Herpes Zoster and its complications | Journal of Infection |
| D. S. Weitzman, O.:Cohen, R.:Chodick, G.:Shalev, V. | 2012 | Epidemiology of herpes zoster and its complication: A population based study in Israel | Pharmacoepidemiology and Drug Safety |
| **Article uses same data as study included in review** | M. Bigby | 2001 | A population-based estimate of the prevalence of postherpetic neuralgia after herpes zoster | Archives of Dermatology |
| D. Bouhassira, O. Chassany, J. Gaillat, G. Gavazzi, T. Hanslik, O. Launay, C. Mann, C. Rabaud, O. Rogeaux and C. Strady | 2010 | Increased burden of zoster and its complications in elderly people | European Geriatric Medicine |
| M. B. Drolet, M.:Levin, M. J.:Schmader, K. E.:Oxman, M. N.:Johnson, R. W.:Camden, S.:Mansi, J. A. | 2010 | A prospective study of the herpes zoster severity of Illness | Clinical Journal of Pain |
| M. L. Haanpaa, P. A. Laippala and T. J. Nurmikko | 1999 | Thermal and tactile perception thresholds in acute herpes zoster | Eur J Pain |
| S. P. Helgason, G.:Gudmundsson, S. | 2001 | Post-herpetic neuralgia was not frequent or severe after a first episode of herpes zoster | Evidence-Based Medicine |
| C. Rabaud, O. Rogeaux, O. Launay, C. Strady, C. Mann, O. Chassany, D. Bouhassira and J. Gaillat | 2013 | Early antiviral treatment fails to completely prevent herpes-related pain | Medecine et Maladies Infectieuses |
| **PHN not an outcome** | K. S. Ammer, T.:Melnizky, P. | 2001 | Thermal imaging in acute herpes zoster or post-zoster neuralgia | Skin Research and Technology |
| K. R. F. Beutner, D. J.:Forszpaniak, C.:Andersen, P. L.:Wood, M. J. | 1995 | Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults | Antimicrobial Agents and Chemotherapy |
| D. Bowsher | 1992 | Acute herpes zoster and postherpetic neuralgia: Effects of acyclovir and outcome of treatment with amitriptyline | British Journal of General Practice |
| A. M. Cebrian-Cuenca, J. Diez-Domingo, M. S. Rodriguez, J. Puig-Barbera, J. Navarro-Perez and C. Herpes Zoster Research Group of the Valencian | 2010 | Epidemiology of herpes zoster infection among patients treated in primary care centres in the Valencian community (Spain) | BMC Family Practice |
| U. Di Luzio Paparatti, F. Arpinelli and G. Visona | 1999 | Herpes zoster and its complications in Italy: An observational survey | Journal of Infection |
| K. Galil, P. W. Choo, J. G. Donahue and R. Platt | 1997 | The sequelae of herpes zoster | Archives of Internal Medicine |
| N. Haas, E. Holle, B. Hermes and B. M. Henz | 2001 | Acute herpes zoster neuralgia: Retrospective analysis of clinical aspects and therapeutic responsiveness | Dermatology |
| K. M. Higa, M.:Hirata, K.:Hori, K.:Manabe, H.:Dan, K. | 1997 | Severity of skin lesions of herpes zoster at the worst phase rather than age and involved region most influences the duration of acute herpetic pain | Pain |
| K. N. Higa, B.:Manabe, H.:Sato, S.:Dan, K. | 1992 | T-lymphocyte subsets in otherwise healthy patients with herpes zoster and relationships to the duration of acute herpetic pain | Pain |
| H. Manabe, K. Dan and K. Higa | 1995 | Continuous epidural infusion of local anesthetics and shorter duration of acute zoster-associated pain | Clinical Journal of Pain |
| D. Moulin | 2006 | Does acute pain associated with herpes zoster respond to treatment with gabapentin? | Nature Clinical Practice Neurology |
| E. M. J. Nagasako, R. W.:Griffin, D. R. J.:Dworkin, R. H. | 2002 | Rash severity in herpes zoster: Correlates and relationship to postherpetic neuralgia | Journal of the American Academy of Dermatology |
| M. L. A. Quinlivan, K. L.:Kelly, P. J.:Parker, S. P.:Scott, F. T.:Johnson, R. W.:Maple, C.:Breuer, J. | 2011 | Persistence of varicella-zoster virus viraemia in patients with herpes zoster | Journal of Clinical Virology |
| M. J. W. Zaal, H. J. Volker-Dieben and J. D'Amaro | 2000 | Risk and prognostic factors of postherpetic neuralgia and focal sensory denervation: A prospective evaluation in acute herpes zoster ophthalmicus | Clinical Journal of Pain |
| **No risk factors of interest** | P. G. M. Kennedy, P.:Scott, F.:Grinfeld, E.:Ashrafi, G. H.:Breuer, J.:Rowan, E. G. | 2013 | Varicella-zoster viruses associated with post-herpetic neuralgia induce sodium current density increases in the ND7-23 Nav-1.8 neuroblastoma cell line | PLoS ONE [Electronic Resource] |
| A. Srebrnik, R. Brandsen and S. Brenner | 1991 | Corticosteroid treatment in the prevention of postherpetic neuralgia | Journal of Dermatological Treatment |
| A. P. Winnie and P. W. Hartwell | 1993 | Relationship between time of treatment of acute herpes zoster with sympathetic blockade and prevention of post-herpetic neuralgia: Clinical support for a new theory of the mechanism by which sympathetic blockade provides therapeutic benefit | Regional Anesthesia |
| **No effect estimates for risk factors of interest (including where the only risk factor was age, and the effect of age was not described as a continuous variable)** | J. Bruxelle | 1995 | Prospective epidemiologic study of painful and neurologic sequelae induced by herpes zoster in patients treated early with oral acyclovir | Neurology |
| A. Colding | 1973 | Treatment of pain: organization of a pain clinic: treatment of acute herpes zoster | Proceedings of the Royal Society of Medicine |
| E. Epstein | 1981 | Treatment of herpes zoster and postzoster neuralgia by subcutaneous injection of triamcinolone | International Journal of Dermatology |
| H. M. L. Oh, A. Y. L. Ho, S. K. Chew and E. H. Monteiro | 1997 | Clinical presentation of herpes zoster in a Singapore hospital | Singapore Medical Journal |
| J. G. J. Pierik, P. D. Gumbs, S. A. C. Fortanier, P. C. E. Van Steenwijk and M. J. Postma | 2012 | Epidemiological characteristics and societal burden of varicella zoster virus in the Netherlands | BMC Infectious Diseases |
| B. P. Yawn, P. Saddier, P. C. Wollan, J. L. St. Sauver, M. J. Kurland and L. S. Sy | 2007 | A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction | Mayo Clinic Proceedings |
| R. Baron, G. Haendler and H. Schulte | 1997 | Afferent large fiber polyneuropathy predicts the development of postherpetic neuralgia | Pain |
| H. Bricout, E. Perinetti, P. Marchettini, P. Ragni, C. Zotti, G. Gabutti, A. Volpi and E. Franco | 2013 | Predictor factors for the presence of post herpetic neuralgia at 3 months in herpes zoster patients aged 50 and over in Italy: Results from a gp-based observational prospective multicenter study | Value in Health |
| G. R. Brown | 1976 | Herpes zoster: correlation of age, sex, distribution, neuralgia, and associated disorders | Southern Medical Journal |
| R. H. Dworkin | 2000 | Prediction and prevention of postherpetic neuralgia | Pain Clinic |
| E. Franco, E. Perinetti, P. Marchettini, P. Ragni, C. Zotti, G. Gabutti, A. Volpi and H. Bricout | 2013 | Proportion of post herpetic neuralgia among patients with herpes zoster in Italy-A multicenter prospective observational study | European Geriatric Medicine |
| E. H. Garbe, K.:Kemper, L.:Reinhard, M.:Behr, S.:Schink, T.:Bricout, H. | 2013 | Incidence of herpes zoster herpes zoster related manifestations and complications in Germany-A retrospective cohort database study from 2005 to 2009 | European Geriatric Medicine |
| E. G. Granell, M.:Nunez, F.:Rius, C.:Catala, E.:De Juan Delago, M.:Gomez-Anson, B. | 2013 | Glial dysfunction may occur early in the brain of patients with neuropathic pain: A 1H-MRS study | Neuroradiology |
| S. S. Han, C. H. Jung, S. C. Lee, H. J. Jung and Y. H. Kim | 2010 | Does skin temperature difference as measured by infrared thermography within 6 months of acute herpes zoster infection correlate with pain level? | Skin Research & Technology |
| S. Imafuku, J. Nakayama, K. Higa, M. Furue, M. Takahara, I. Katayama and M. Tani | 2013 | One-year follow-up of zoster-associated pain in 764 patients with acute herpes zoster treated using famciclovir | Journal of Investigative Dermatology |
| J. I. McGill and J. E. White | 1994 | Acyclovir and post-herpetic neuralgia and ocular involvement | BMJ |
| W. Meister, A. Neiss, G. Gross, H. W. Doerr, W. Hobel, J. P. Malin, J. Von Essen, B. Y. Reimann, C. Witke and P. Wutzler | 1998 | A prognostic score for postherpetic neuralgia in ambulatory patients | Infection |
| Z. R. Mok and H. H. Tan | 2013 | Herpes zoster: A review of cases seen at the National Skin Center, Singapore (2008-2010) | Journal of the American Academy of Dermatology |
| C. Mondelli, S. Romano, P. Passerv, A. Delia Porta and P. Rossi | 1996 | Effects of acyclovir on sensory axonal neuropathy, segmental motor paresis and postherpetic neuralgia in herpes zoster patients | European Neurology |
| S. D. Nithyanandam, S.:Stephen, J.:Joseph, M. | 2009 | Eruption severity and characteristics in herpes zoster ophthalmicus: Correlation with visual outcome, ocular complications, and postherpetic neuralgia | International Journal of Dermatology |
| M. L. A. Quinlivan, K.:Ran, H.:McElwaine, S.:Leedham-Green, M.:Scott, F. T.:Johnson, R. W.:Breuer, J. | 2007 | Effect of viral load on the outcome of herpes zoster | Journal of Clinical Microbiology |
| J. M. Riopelle, M. Naraghi and K. P. Grush | 1984 | Chronic neuralgia incidence following local anesthetic therapy for herpes zoster | Archives of Dermatology |
| R. S. Rogers, 3rd and J. P. Tindall | 1971 | Geriatric herpes zoster | J Am Geriatr Soc |
| H. Yanagida, K. Suwa and G. Corssen | 1987 | No prophylactic effect of early sympathetic blockade on postherpetic neuralgia | Anesthesiology |
| **Effect estimates for risk factors of interest are not age-adjusted (exclusion criteria not applied to studies on genetic risk factors)** | D. S. Borkar, V. M. Tham, E. Esterberg, K. J. Ray, A. C. Vinoya, J. V. Parker, A. Uchida and N. R. Acharya | 2013 | Incidence of herpes zoster ophthalmicus: results from the Pacific Ocular Inflammation Study | Ophthalmology |
| D. Bowsher | 1999 | The lifetime occurrence of Herpes zoster and prevalence of post-herpetic neuralgia: A retrospective survey in an elderly population | European Journal of Pain |
| J. Decroix, H. Partsch, R. Gonzalez, H. Mobacken, C. L. Goh, J. B. Walsh, S. Shukla and B. Naisbett | 2000 | Factors influencing pain outcome in herpes zoster: An observational study with valaciclovir | Journal of the European Academy of Dermatology and Venereology |
| R. H. Dworkin, R. J. Boon, D. R. G. Griffin and D. Phung | 1998 | Postherpetic neuralgia: Impact of famciclovir, age, rash severity, and acute pain in herpes zoster patients | Journal of Infectious Diseases |
| R. H. Dworkin, G. Hartstein, H. L. Rosner, R. R. Walther, E. W. Sweeney and L. Brand | 1992 | A high-risk method for studying psychosocial antecedents of chronic pain: The prospective investigation of herpes zoster | Journal of Abnormal Psychology |
| I. B. Engberg, G. B. Grondahl and K. Thibom | 1995 | Patients' experiences of herpes zoster and postherpetic neuralgia | Journal of advanced nursing |
| A. Gauthier, J. Breuer, D. Carrington, M. Martin and V. Remy | 2009 | Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom | Epidemiology and Infection |
| L. E. Gialloreti, M. Merito, P. Pezzotti, L. Naldi, A. Gatti, M. Beillat, L. Serradell, R. di Marzo and A. Volpi | 2009 | Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: A retrospective, population-based study | BMC Infectious Diseases |
| C. L. Goh and L. Khoo | 1997 | A retrospective study of the clinical presentation and outcome of herpes zoster in a tertiary dermatology outpatient referral clinic | International Journal of Dermatology |
| M. Haanpaa, P. Dastidar, A. Weinberg, M. Levin, A. Miettinen, A. Lapinlampi, P. Laippala and T. Nurmikko | 1998 | CSF and MRI findings in patients with acute herpes zoster | Neurology |
| M. H. Haanpaa, V.:Nurmikko, T. | 1997 | Motor involvement in acute herpes zoster | Muscle and Nerve |
| M. Hadi Aziz Jalali, H. Ansarin and R. Soltani-Arabshahi | 2006 | Broad-band ultraviolet B phototherapy in zoster patients may reduce the incidence and severity of postherpetic neuralgia | Photodermatology Photoimmunology and Photomedicine |
| S. P. Harding, J. R. Lipton and J. C. Wells | 1987 | Natural history of herpes zoster ophthalmicus: predictors of postherpetic neuralgia and ocular involvement | Br J Ophthalmol |
| K. Hillebrand, L. Kemper, R. Schulze-Rath, T. Schink and E. Garbe | 2013 | Incidences of herpes zoster, its manifestations and complications for 2005-2009 in Germany-a retrospective cohort study | Pharmacoepidemiology and Drug Safety |
| R. E. Hope-Simpson | 1975 | Postherpetic neuralgia | The Journal of the Royal College of General Practitioners |
| M. Kolsek | 2012 | TENS - an alternative to antiviral drugs for acute herpes zoster treatment and postherpetic neuralgia prevention | Swiss Medical Weekly |
| J. S. H. A. Koopman, J. P. Dieleman, F. J. Huygen, M. de Mos, C. G. M. Martin and M. C. J. M. Sturkenboom | 2009 | Incidence of facial pain in the general population | Pain |
| I. Kurokawa, K. Kumano and K. Murakawa | 2002 | Clinical correlates of prolonged pain in Japanese patients with acute herpes zoster | Journal of International Medical Research |
| I. Kurokawa, K. Murakawa and K. Kumano | 2007 | The change in zoster-associated pain treated with oral valaciclovir in immunocompetent patients with acute herpes zoster | International Journal of Clinical Practice |
| W. Lapolla, C. DiGiorgio, K. Haitz, G. Magel, N. Mendoza, J. Grady, W. Lu and S. Tyring | 2011 | Incidence of postherpetic neuralgia after combination treatment with gabapentin and valacyclovir in patients with acute herpes zoster: Open-label study | Archives of Dermatology |
| J. P. Malin | 1993 | A retrospective and an observational study with acyclovir | Journal of medical virology |
| S. C. Martin, V.:Gabriele, W.:Jennifer, L.:Andreas, B.:Birgitt, G.:Karin, K. | 2012 | Intravenous vitamin C in the treatment of shingles | European Journal of Integrative Medicine |
| S. Ogawa, H. Suzuki, H. Saitoh, S. Saeki, J. Katoh, Y. Noda, T. Nakamura, K. Noda and T. Suzuki | 1993 | Risk factors for developing post-herpetic neuralgia: A retrograde analysis of 232 patients | Pain Clinic |
| Petersen, K. L.:Rowbotham, M. C. | 2010 | Natural history of sensory function after herpes zoster | Pain |
| M. W. Ragozzino, L. J. Melton, 3rd, L. T. Kurland, C. P. Chu and H. O. Perry | 1982 | Population-based study of herpes zoster and its sequelae | Medicine |
| V. S. Schafer, T. A. Kermani, C. S. Crowson, G. G. Hunder, S. E. Gabriel, S. R. Ytterberg, E. L. Matteson and K. J. Warrington | 2010 | Incidence of herpes zoster in patients with giant cell arteritis: A population-based cohort study | Rheumatology |
| M. Schencking, C. Vollbracht, G. Weiss, J. Lebert, A. Biller, B. Goyvaerts and K. Kraft | 2012 | Intravenous vitamin C in the treatment of shingles: Results of a multicenter prospective cohort study | Medical Science Monitor |
| F. T. Scott, M. E. Leedham-Green, W. Y. Barrett-Muir, K. Hawrami, W. J. Gallagher, R. Johnson and J. Breuer | 2003 | A study of shingles and the development of postherpetic neuralgia in east London | Journal of Medical Virology |
| H. G. R. Thyregod, M. C.:Peters, M.:Possehn, J.:Berro, M.:Petersen, K. L. | 2007 | Natural history of pain following herpes zoster | Pain |
| B. M. A. Veetil, E. L. Matteson, S. E. Gabriel and C. S. Crowson | 2011 | Incidence and time trends of herpes zoster in rheumatoid arthritis: A population based cohort study | Arthritis and Rheumatism |
| B. M. A. Veetil, E. Myasoedova, E. L. Matteson, S. E. Gabriel, A. B. Green and C. S. Crowson | 2013 | Incidence and time trends of herpes zoster in rheumatoid arthritis: A population-based cohort study | Arthritis Care and Research |
| R. J. Whitley, S. Shukla and R. J. Crooks | 1998 | The identification of risk factors associated with persistent pain following herpes zoster | J Infect Dis |
| R. J. Whitley, H. L. Weiss, S. J. Soong and J. W. Gnann | 1999 | Herpes zoster: risk categories for persistent pain | Journal of Infectious Diseases |
| Q. Xing, D. Hu, F. Shi and F. Chen | 2013 | Role of regulatory T cells in patients with acute herpes zoster and relationship to postherpetic neuralgia | Arch Dermatol Res |
| M. M. Zak-Prelich, R. C.:Sysa-Jedrzejowska, A.:Norval, M. | 2003 | Local immune responses and systemic cytokine responses in zoster: Relationship to the development of postherpetic neuralgia | Clinical and Experimental Immunology |
| S. M. L. Zhu, Y. M.:An, E. D.:Chen, Q. L. | 2009 | Influence of systemic immune and cytokine responses during the acute phase of zoster on the development of postherpetic neuralgia | Journal of Zhejiang University: Science B |
| **Full text not in English** | Y. W. Yamasaki, K.:Kitagawa, K.:Fukuda, T. | 1990 | Treatment of herpes virus infection using antiviral agents 2. Treatment of herpes zoster with intravenous administration of Ara A | IRYO - Japanese Journal of National Medical Services |
| **Data provided on effect estimates appear incorrect** | Nurmikko, T. J.:Rasanen, A.:Hakkinen, V. | 1990 | Clinical and neurophysiological observations on acute herpes zoster | Clinical Journal of Pain |

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| **Table A2: Sub group meta-analyses to identify causes of heterogeneity for effect of age and gender on PHN.** |
|  | **No. of studies** | **Summary RR (95% CI)** | **Pheterogeneity; I²** | **P-value from meta-regression (univariate)** |
| **Age**  |  |  |  |  |
| All studies | 8 | - | P=0.029; 55.1% | - |
|  |  |  |  |  |
| Mean age of study population  |  |  |  |  |
| ≥60 years | 3 | 2.39 (1.81-3.16) | P=0.533; 0.0% |  |
| <60 years | 3 | 1.46 (1.24-1.73) | P=0.242; 29.4% | 0.08 |
| Definition of PHN |  |  |  |  |
| Pain at 4 months | 3 | 1.45 (1.21-1.73) | P=0.195; 38.9% |  |
| Pain at 3 months | 3 | 1.80 (1.48-2.20) | P=0.305; 15.8% | 0.52 |
| Ascertainment of PHN |  |  |  |  |
| Self-reported | 6 | 1.63 (1.44-1.85) | P=0.079; 49.3% |  |
| Medical records | 1 | 3.11 (1.82-5.31) | - | 0.14 |
| Excluded immunosuppressed |  |  |  |  |
| Yes | 2 | 1.41 (1.18-1.68) | P=0.235; 29.1% |  |
| No | 4 | 1.96 (1.62-2.37) | P=0.126; 47.6% | 0.23 |
| Source population from primary care |  |  |  |  |
| Yes | 5 | 1.97 (1.67-2.33) | P=0.188; 35.0% |  |
| No | 2 | 1.39 (1.15-1.68) | P=0.186; 42.8% | 0.18 |
|  |  |  |  |  |
|  |  |  |  |  |
| **Gender** |  |  |  |  |
| All studies | 7 | - | P=0.01; 73.9% | - |
|  |  |  |  |  |
| Mean age of study population  |  |  |  |  |
| ≥60 years | 2 | 0.62 (0.40-0.95) | P=0.335; 0.0% |  |
| <60 years | 3 | 1.65 (1.19-2.30) | P=0.364; 1.0% | 0.04 |
| Definition of PHN |  |  |  |  |
| Pain at 4 months | 1 | 2.01 (1.28-3.16) | - |  |
| Pain at 3 months | 3 | 0.68 (0.47-0.99) | P=0.013; 77.0% | 0.45 |
| Ascertainment of PHN |  |  |  |  |
| Self-reported | 6 | 1.13 (0.88-1.44) | P=0.000; 78.1% |  |
| Medical records | 1 | 0.90 (0.38-2.16) | - | 0.83 |
| Excluded immunosuppressed |  |  |  |  |
| Yes | 1 | 2.01 (1.28-3.16) | - |  |
| No | 6 | 0.88 (0.66-1.16) | P=0.018; 63.5% | 0.25 |
| Source population from primary care |  |  |  |  |
| Yes | 3 | 0.78 (0.53-1.15) | P=0.020; 74.5% |  |
| No | 3 | 1.36 (0.93-1.99) | P=0.006; 80.4% | 0.97 |

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| **Table A3: Association between PHN and various risk factors: risk factors, adjusted effect measure and 95% confidence interval by study. All risk factors included in the final multivariate model are listed, unless otherwise specified** |
|  | **PHN definition** | **Age** **(in years)** | **Gender** | **Severe immune suppression** | **Other physical or psychological comorbidities** | **Genetic or lifestyle risk factors** | **Other “non-vaccine targetable” risk factors in final model** |
| **Cohort studies - risk factor: odds ratio (95% CI) unless specified** |
| Cebrián-Cuenca2011²  | 3m(main results) | Per yr increase: 1.04 (CI 1.01-1.08, P<0.03) | Gender: OR not given P>0.05 | ² | ² | ² | Antiviral use: OR not reported P>0.05. ² |
|  | 1m | Per yr increase: 1.04 (CI not given, P<0.01) | Gender: OR not given P>0.05 | ² | ² | ² | Time interval (days) between symptom onset and clinical diagnosis: 1.11, P<0.01Antiviral use: OR not reported P>0.05. ² |
| Coen 2006 | 3m (main results) | Age over 50 yrs: 3.91 (1.38-11.11) | F vs M: 2.45 (0.96-6.23) | - | - | - | Extent of rash score: not associated, ophthalmic branch involvement: 3.20 (1.19-8.55), VAS >5: 3.92 (1.33-11.5), VAS>5 and or age over 50: 8.51 (1.11-65.2), time from onset of rash (days): 0.93 (0.80-1.07). |
|  | 6m | Age over 50 years:13.8 (1.74-110) | F vs M: 5.21 (1.38-19.6) | - | - | - | Extent of rash score: not associated, ophthalmic branch involvement: 5.31 (1.66-16.9), VAS >5: 3.68 (1.01-13.5), VAS>5 and or age over 50: 4.74 (1.59-38.2), time from onset of rash (days): 0.78 (0.61-1.00). |
| Drolet 2010 | 3m (main results) | Per yr increase:RR1.02 (1.00-1.04)  | Not in final model: No association in univariate analyses | General immune suppression (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 1.09 (1.01-1.18)Not in final model: No association with having another pain condition or other pre-zoster EQ-5D measures in univariate analyses. | 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)Not in final model: No association with working status or education in univariate analyses. | Severe acute pain at zoster: RR 2.06 (0.98-4.35) |
|  | 30 days(RRs not reported)  | Older age associated with PHN | - | - | **-** | - | Severe acute pain at zoster associated with PHN Limitation in performing usual activities at recruitment associated with PHN |
| Helgason2000  | 3m (main results) | Per 10 yr increase:2.11 (1.56-2.84) | Not in final model: No association in univariate analyses | - | **-** | - | - |
|  | 1m | 1.87 (1.56 to 2.23) | Not in final model: No association in univariate analyses | - | **-** | - | - |
|  | 6m | 2.45 (1.50-4.01) | Not in final model: No association in univariate analyses | - | **-** | - | - |
|  | 12m | 2.33 (1.48-3.69 | Not in final model: No association in univariate analyses | - | **-** | - | - |
| NB: Reference category listed last. yr=year, SLE=Systemic Lupus Erythematosus ¹PCS=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) ²Variables included in the final model, and whether the final model was restricted to immunocompetent patients, is unclear. ³Adjusted for age and gender only ⁴Study used ordered logistic regression, therefore the parameters represent the exposure ORs for being the highest outcome categories, compared to the lowest outcome categories: it is assumed the effect of exposure is the same for all splits of the outcome categories. ⁵Physical Health measured using the Life Stressors and Social Resources Inventory, which sums the total number of patient reported medical conditions. |

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| **Table A3: (continued)** |
|  | **PHN definition** | **Age****(in years)** | **Sex** | **Severe immune suppression** | **Other physical or psychological comorbidities** | **Genetic or lifestyle risk factors** | **Other risk factors in final model** |
| Cohort studies (continued) |
| Kotani2004  | 2m | Per 10 yr increase: 2.2 (1.1-4.5) | Not in final model(no association in univariate analyses) | - | Not in final model: no association with diabetes, malignancy or autoimmune disease in univariate analyses | - | - |
|  | 6m | Per 10 yr increase: 2.7 (1.2-5.7) | Not in final model(no association in univariate analyses) |  | Not in final model: no association with diabetes, malignancy or autoimmune disease in univariate analyses |  |  |
|  | 12m | Per 10 yr increase: 2.7 (1.2-6.2) | Not in final model(no association in univariate analyses) |  | Not in final model: no association with diabetes, malignancy or autoimmune disease in univariate analyses |  |  |
| Opstelten 2002 | 3m | ≤54: 1.0055-74: 5.4 (1.1-26.5)≥75: 19.7(4.3-90.9) | F vs M: 1.0 (0.9-1.0) | - | Diabetes:1.7 (0.5-6.2)Psycho-pharmaceuticals use: 1.4 (0.3-5.6)Not in final model: no association with chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosis, psychological problem or corticosteroid use at zoster diagnosis in univariate analyses. | - | Localization, ophthalmic vs not:2.2 (0.8-6.5), Painful prodrome: 1.2 (0.3-5.6) |
|  | 1m | ≤54: 1.0055-74: 4.2 (1.8-9.7)≥75: 10.7(4.6-25.1) | F vs M: 0.8 (0.4-1.5) | - | Diabetes:1.4 (0.6-3.8)Psycho-pharmaceuticals use: 1.4 (0.5-3.9)Not in final model: no association with chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosis, psychological problem or corticosteroid use at zoster diagnosis in univariate analyses. | - | Localization, ophthalmic vs not:2.3 (1.1-4.6), Painful prodrome: 2.1 (0.9-5.2) |
| Opstelten 2007 | 3m | Per y:1.08 (1.04-1.12) | Not in final model: No association in univariate analyses | - | Trust in healthcare score, 1 unit increase from 0-100: 1.01 (1.00-1.03)Not in final model: psychological predictors not associated in univariate analyses.  |  - | Duration of rash prior to consultation, in d: 0.78 (0.64-0.97), Severe rash, ≥43 vesicles: 2.31 (1.16-4.58), Severity of acute pain, per vAS unit: 1.02 (1.01-1.03) |
|  | 1m (ORs not available) | Same as above, except age not associated with PHN and epidural injection was associated with PHN. |
| Parruti2010  | 1-3m | Per 10 y increase:1.01 (0.99-1.02) | F vs M: 1.39 (0.84-2.30) | Not in final model: No association with HIV in univariate analyses.  | Trauma at site of lesion:2.53 (1.37-4.65)Surgical Intervention at site of lesion: 1.33 (0.79-2.25)Not in final model: no association with HCV infection, hypertension, diabetes, neoplasm, neurological disorders, psychiatric illness, allergy or family history of major cardiovascular events, malignancies, neurological diseases, major depression, at univariate analysis. | Current/former smoking: 2.08 (0.22-3.55)Not in final model: no association with alcohol abuse, familial status, educational level in univariate analyses. | Intense/very intense pain at presentation:2.19 (1.32-3.65), Missed antiviral prescription: 2.28 (1.04-4.98) |
|  | 1 month | Per 10 y increase:1.01 (1.00-1.02) | F vs M: 1.05 (0.68-1.63) | Not in final model: No association with HIV in univariate analyses. | Trauma at site of lesion:2.22 (1.12-4.39)Surgical Intervention at site of lesion: 1.60 (0.98-2.63)Not in final model: no association with HCV infection, hypertension, diabetes, neoplasm, neurological disorders, psychiatric illness, allergy or family history of major cardiovascular events, malignancies, neurological diseases, major depression, at univariate analysis. | Current/former smoking: 1.62 (0.98-2.67)Not in final model: no association with alcohol abuse, familial status, educational level in univariate analyses. | Intense/very intense pain at presentation:2.41 (1.43-4.04), Missed antiviral prescription: 2.01 (1.01-4.96) |
| **Case base studies - risk factor: prevalence ratio (95% confidence interval)** |
| Choo1997††  | 60 days | 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)Corticosteroid exposure prior to zoster: 1.4 (0.3-6.0) | - | Prodromal symptoms: 3.4 (1.3-9.1).[In final model, but no evidence of association with PHN in multivariate analysis (confidence intervals overlapped the null): number of encounters previous 180d, dermatome affected, interference with activities on daily living, complications including superinfection and ocular complications and other, acyclovir exposure, corticosteroid exposure after zoster] |
|  | 30 days | Per y:1.09 (1.06-1.12) | F vs M:1.3 (0.6-2.7) | Connective tissue disease, HIV infection or organ allograft: 3.1 (1.0-9.5) | Diabetes: 2.1 (0.6-7.7)Cancer: 0.2 (0.1-0.8)Corticosteroid exposure prior to zoster: 2.9 (0.7-11.3) | - | Prodromal symptoms: 2.1 (1.1-4.3). [In final model, but no evidence of association with PHN in multivariate analysis (confidence intervals overlapped the null): number of encounters previous 180d, dermatome affected, interference with activities on daily living, complications including superinfection and ocular complications and other, acyclovir exposure, corticosteroid exposure after zoster] |
| NB: Reference category listed last. Yr=year, HCV=Hepatitis C virus, APOE=alipoprotien E. ††Adjusted for age (continuous variable), presence (yes or no) of prodromal symptoms, severe pain, or comorbid conditions; and number of healthcare encounters. |

| **Table A4:** Assessment of bias: detailed notes |
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|  | **Confounding** | **Selection Bias** | **Exposure information bias** | **Outcome (PHN) information bias** | **Bias due to missing data** |
| **Type of bias** | **Residual confounding by age** | **Loss to follow-up** | **Non-differential misclassification** | **Reporting bias** | **Non-differential misclassification** | **Missing exposure data** |
| **Cohort studies** |
| **Asada****2013** | **🞆** | **🞆** | **🞆** | **🞆** | **?** | **◆** |
|  | Age adjusted using categorical variable (50-, 60-, 70, ≥80) | 4% of cohort lost to follow-up | Several dermatologists collected exposure information: differences between physician recording practices may lead to different exposure ascertainment | -Outcome assessed using a standard scale for pain -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status assessment.  | Definition of pain may vary between patients | Over half patients had missing data for VZV skin test reaction tests; Impact of missing data not presented.  |
|  |  |  |  |  |  |  |
| **Bouhassira 2012** | **◆** | **◼** | **🞆** | **🞆** | **?** | **?** |
| Age adjusted using binary variable  | 20% of cohort lost to follow-up: no information on non-responders | Several risk factors assessed: some errors are possible | -Outcome assessed using a standard question -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status | Definition of pain may vary between patients | Missing data not described for all exposure variables; 36% of PHN patients and 28% non-PHN patients missing data on depression. Impact of missing data not presented. |
|  |
| **Cebrián-Cuenca****2011** | **🞆** | **◼** | **🞆** | **🞆** | **?** | **🞆** |
| Age adjusted using continuous variable | 15% of cohort lost to follow-up | Some information from medical record review; differences between physician recording practices may lead to different exposure ascertainment | -Outcome ascertained from patient reported pain symptoms -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status | Definition of pain may vary between patients | No missing data |
|  |
| **Coen****2006** | **◆** | **🞆** | **?** | **🞆** | **?** | **?** |
| Age adjusted using binary variable | 3% of cohort lost to follow-up | Unclear who collected exposure data | -Outcome ascertained from patient reported pain symptoms -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status | Definition of pain may vary between patients | Missing data not reported for all exposure variables |
|  |
| **Drolet 2010**  | **🞆** | **🞆** | **🞆** | **🞆** | **?** | **◼** |
| Age adjusted using continuous variable | No loss to follow-up | Several risk factors assessed: some errors are possible | -Outcome assessed using a standard questionnaire -Unclear if patients were aware of study hypothesis  | Definition of pain may vary between patients | Missingness reported if exposures had 10 + missing values. Income missing for 28 patients (11%); included missing category in analyses which may cause bias. |
|  |
| **Haanpaa****2000** | **🞆** | **◼** | **🞆** | **◼** | **?** | **?** |
|  | Age adjusted using continuous variable | 18% of cohort lost to follow-up | Unclear how age and sex were assessed, however unlikely to be misclassified  | -Outcome ascertained from patient reported pain symptoms -Study investigator those ascertaining outcome was aware of exposure status | Definition of pain may vary between patients | Missing data not reported for all exposure variables |
|  |  |  |  |  |  |  |
| **Helgason****2000** | **🞆** | **🞆** | **🞆** | **🞆** | **?** | **🞆** |
| Not applicable: no multivariable analysis | 7% of cohort loss to follow-up: no information on non-responders | Unclear how age and sex were assessed, however unlikely to be misclassified  | -Outcome ascertained from patient reported pain symptoms -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status | Definition of pain may vary between patients | No missing data |
|  |
| **Jih****2009** | **◆** | **?** | **?** | **◆** | **◆** | **?** |
| Age adjusted using binary variable  | Unclear if any zoster patients were lost to follow-up during 90d following zoster episode: e.g. patients may have moved or died.  | Based on claims data where coding has not been validated: possibility of exposure information being rule-out codes (e.g. unusually high rate of diabetes (20.6%) in the study population). | -Physicians recording PHN not aware of study hypothesis -Ascertainment bias: Patients with exposures (e.g. diabetes) may have higher medical attendance than healthy zoster patients, thus more likely to be ascertained in claims data, a spurious association | No ICD-9 code for PHN, therefore based on zoster code plus neuralgia treatment. Physicians may have various other ways of recording PHN.  | Missing data not reported |
|  |  |  |  |  |  |  |
| **Jung****2004** | **🞆** | **◼** | **🞆** | **🞆** | **?** | **🞆** |
|  | Age adjusted using continuous variable | 11% of cohort lost to follow-up: generally comparable to those with complete data, except being on average 4 years younger | Unlikely | -Outcome ascertained from patient reported pain symptoms-Patients originally recruited into clinical trial of antiviral effectiveness thus unlikely to be influenced by these study hypotheses | Definition of pain may vary between patients | Missing data not available: likely to be minimal (from email correspondence)  |
|  |  |  |  |  |  |  |
| **Kanbayashi****2012** | **◆** | **🞆** | **◆** | **?** | **◆** | **🞆** |
|  | Age adjusted using categorical variable (<50, 51-74, ≥75) | No loss to follow-up  | Exposure information from clinical records; differences between physician recording practices may lead to different exposure ascertainment. Furthermore, it is unclear whether this initial visit, when exposures were defined, is for acute zoster or whether these patients already have PHN. | -Unclear how pain defined, however ascertainment bias possible: i.e. patients with exposures (e.g. diabetes) may have higher medical attendance than healthy zoster patients, thus more likely to be diagnosed with PHN, causing a spurious association-Physicians recording PHN not aware of study hypothesis  | PHN was ascertained from medical record of documented pain: clinicians may record symptoms differently | No missing data reported |
|  |  |  |  |  |  |  |
| **Katz** **2005** | **🞆** | **🞆** | **◼** | **◼** | **?** | **🞆** |
|  | Age adjusted using continuous variable | 8% of cohort lost to follow-up: no major differences in exposures compared to those completing follow-up | Several risk factors assessed: some errors are possible. Exposures recorded on average 17 days following rash onset: measures of pre-morbid functioning may be biased | -Outcome ascertained from patient reported pain symptoms-Some outcome assessments carried out by psychologist aware of exposure status -Unclear if patients aware of study hypotheses | Definition of pain may vary between patients | Missing exposure data imputed for multivariate analyses: similar results obtained with complete case analysis  |
|  |  |  |  |  |  |  |
| **Kotani****2004** | **🞆** | **🞆** | **?** | **?** | **?** | **?** |
|  | Age adjusted using categorical variable (per 10year increase) | No loss to follow-up  | Method of ascertaining exposures is unclear | -Unclear how pain was ascertained-Unclear if interviewers know exposure status -Unclear if patients aware of study hypotheses | Definition of pain may vary between patients | Missing data not reported |
|  |  |  |  |  |  |  |
| **Opstelten 2002** | **◆** | **🞆** | **🞆** | **◆** | **◆** | **◼** |
|  | Age adjusted using categorical variable (≤54, 55-74, ≥75) | No loss to follow-up  | Exposure information from clinical records; differences between physician recording practices may lead to different exposure ascertainment. | -Physicians recording PHN not aware of study hypothesis -Ascertainment bias: Patients with exposures (e.g. diabetes) may have higher medical attendance than healthy zoster patients, thus more likely to be ascertained in claims data, causing a spurious association. Under-capture of PHN likely, indicated by very low incidence of PHN in zoster patients; may be related to exposure status | PHN defined as recording of pain or analgesic; clinicians may record symptoms / prescribe medicine differently | Certain exposures (eg prodromal symptoms) may not be routinely recorded by clinician: more likely to reduce statistical power |
|  |  |  |  |  |  |  |
| **Opstelten 2007** | **🞆** | **🞆** | **🞆** | **🞆** | **?** | **◼** |
|  | Age adjusted using continuous variable | No loss to follow-up  | Unlikely | -Outcome ascertained from patient-completed questionnaire -Unclear if patients aware of study hypotheses | Definition of pain may vary between patients | 127 patients had missing values for ≥1 variables: details of missingness not reported. Missing data was singly imputed |
|  |  |  |  |  |  |  |
| **Park** **2011** | **◆** | **🞆** | **?** | **?** | **?** | **?** |
|  | Age adjusted using binary variable  | No loss to follow-up  | Unclear how exposures assessed | -Unclear how outcome assessed -Unclear if patients aware of study hypotheses | Definition of pain may vary between patients | No information on completeness of exposure data |
|  |  |  |  |  |  |  |
| **Parruti** **2010** | **🞆** | **🞆** | **🞆** | **🞆** | **?** | **◼** |
|  | Age adjusted using categorical variable (per 10 year increase) | 6% of cohort lost to follow-up: no information on non-responders | Unlikely | -Outcome ascertained from patient reported pain symptoms -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status | Definition of pain may vary between patients | Some missing exposure data: impact on findings unclear |
|  |  |  |  |  |  |  |
| **Volpi****2008** | **◆** | **◆** | **🞆** | **🞆** | **?** | **◼** |
|  | Age adjusted using binary variable | 41% of cohort lost to follow-up: no information on non-responders | Unlikely | -Outcome ascertained from patient reported pain symptoms -Unclear if patients were aware of study hypothesis or those ascertaining outcome were aware of exposure status | Definition of pain may vary between patients | Some missing exposure data: impact on findings unclear |
|  |  |  |  |  |  |  |
| **Wozniak****2007** | **🞆** | **?** | **🞆** | **?** | **?** | **🞆** |
|  | Confounding by age n/a in genetic studies: confounding by population possible, yet selected Caucasian patients  | No loss to follow-up  | Objective measures of exposure: unlikely to be biased | -Unclear if researchers are aware of exposure status  | Definition of pain may vary between patients | No missing data not reported |
|  |  |  |  |  |  |  |
| **Case-base study** |
|  | **Residual confounding by age** | **Loss to follow-up and selection of base population** | **Non-differential misclassification** | **Reporting bias** | **Non-differential misclassification** | **Missing exposure data** |
| **Choo****1997** | **🞆** | **🞆** | **🞆** | **◼** | **◼** | **◼** |
|  | Age adjusted as continuous variable | No loss to follow-up reported. Randomly selected non-PHN patients from all eligible zoster patients  | Exposure information from clinical records; differences between physician recording practices may lead to different exposure ascertainment. | Ascertainment bias: Patients with exposures (e.g. diabetes) may have higher medical attendance than healthy zoster patients, thus more likely to be diagnosed with PHN, causing a spurious association. However authors adjusted for healthcare utilisation. | Physicians may have various ways of recording PHN; however authors identified potential PHN cases using a broad criteria, before screening their medical records for evidence of PHN | Certain exposures (eg prodromal symptoms) may not be routinely recorded by clinician: could reduce statistical power |