Herpes zoster

– Occurrence and risk factors –

PhD dissertation

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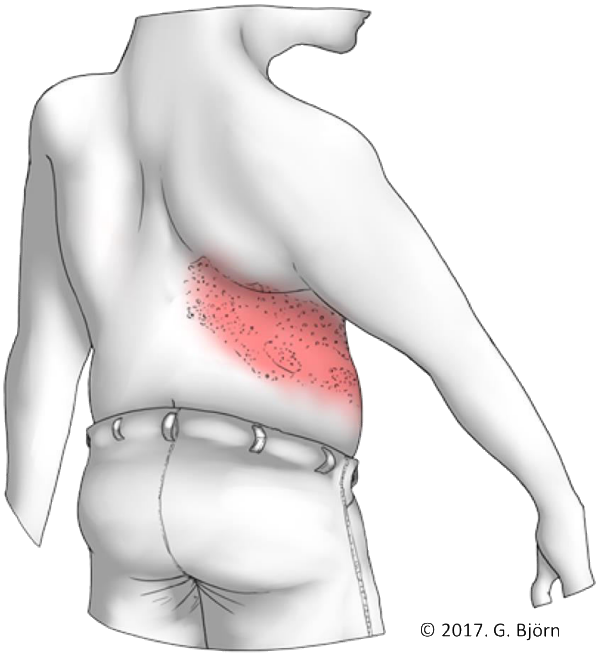

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To my family

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List of papers

The thesis is based on the following original studies, which will be referred to in the text by their roman numerals:

I. Schmidt SA, Vestergaard M, Baggesen LM, Pedersen L, Schønheyder HC, Sørensen HT. Prevaccination epidemiology of herpes zoster in Denmark: quantification of occurrence and risk factors. Submitted

II. Schmidt SA, Vestergaard M, Pedersen HS, Schønheyder HC, Thomas SL, Smeeth L, Mansfield KE, Sørensen HT, Forbes HJ, Langan SM. Partner bereavement and risk of herpes zoster: Results from two population-based case-control studies in Denmark and the United Kingdom. Clin Infect Dis. 2017;64:572–579

III. Schmidt SA, Langan SM, Pedersen HS, Schønheyder HC, Thomas SL, Smeeth L, Mansfield KE, Sørensen HT, Forbes HJ, Vestergaard M. Mood disorders and risk of herpes zoster in two population-based case-control studies in Denmark and the United Kingdom. Submitted

IV. Schmidt SA, Mor A, Schønheyder HC, Sørensen HT, Dekkers OM, Cronin-Fenton D. Herpes zoster as a marker of occult cancer: A systematic review and meta-analysis. J Infect. 2017;74(3):215–235.

Abbreviations

CI	Confidence interval
CKD	Chronic kidney disease
CMI	Cell-mediated immunity
COPD	Chronic obstructive pulmonary disease
CPR	Central personal registration
CPRD	Clinical Practice Research Datalink
DNA	Deoxyribonucleic acid
EMBASE	Biomedical database (Elsevier)
GC	Glucocorticoid
HES	Hospital Episode Statistics database
HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic stem cell transplantation
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases (with version number)
IMD	Index of Multiple Deprivation
MEDLINE	The U.S. National Library of Medicine® (NLM) premier bibliographic database
NHS	National Health Service
OR	Odds ratio
PHN	Post-herpetic neuralgia
PPV	Positive predictive value
PubMed	Search engine providing convenient access to *e.g.*, the MEDLINE database
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
UK	United Kingdom
US	United States
VZV	Varicella-zoster virus
WHO	World Health Organization

Contents

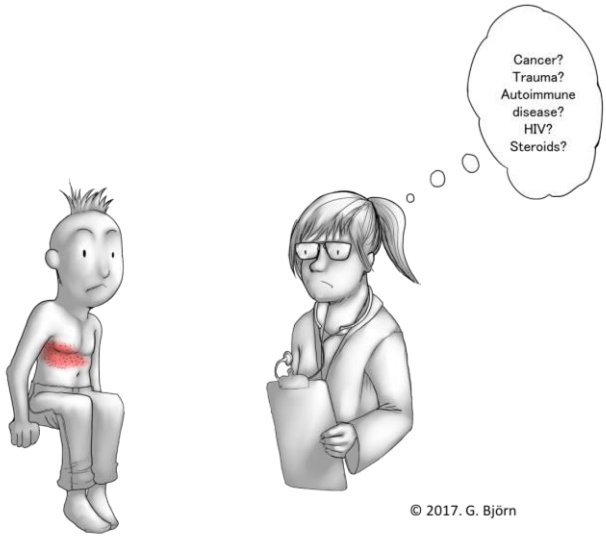
1. Introduction

A 61-year-old man presented to his general practitioner with a painful and itchy belt-like vesicular rash on the right side of the chest and back, corresponding to the T4 dermatome (Figure 1). Rash onset in the previous day had been preceded by 2 days with moderate burning pain in the area. The patient reported no systemic symptoms, except for increasing tiredness over the past couple of months. The patient had had varicella in early childhood. Medical history was notable for cholelithiasis and hypertension, for which he took 10 mg amlodipine daily. No immune-related disease, recent physical trauma, or mental stress was reported. The patient lived with his wife, had two adult children, and was employed in an office job. Alcohol consumption was within recommended limits, but he was overweight and had smoked 40 pack-years since adolescence.

A diagnosis of herpes zoster was made clinically without further laboratory testing. Acyclovir 800 mg five times daily for 8 days was prescribed together with acetaminophen and zinc ointment for pain relief. The herpetic lesions healed without scarring within three weeks.

Thirteen months later, the patient was admitted to the hospital with intermittent pain in the right upper quadrant of the abdomen. Diagnostic imagining on the suspicion of gallstones (also confirmed) revealed a 12-cm tumor in the right kidney. The tumor was removed through complete nephrectomy and pathological examination returned the final diagnosis of clear-cell renal carcinoma.

Figure 1. Consultation for herpes zoster



This case vignette illustrates a typical presentation of herpes zoster to the healthcare professional. In particular, it addresses potential provoking factors, including the controversial topic of whether herpes zoster can be a marker for occult (undiagnosed) cancer. The case serves as a springboard for this thesis, which concerns the epidemiology of herpes zoster.

Herpes zoster is a vaccine-preventable condition, and it is estimated that roughly one-third of the population will develop the disease. Nevertheless, little is known about how common herpes zoster is in Denmark and why some persons develop this condition while others do not. This thesis therefore aims to answer the following: What is the occurrence of herpes zoster in Denmark? Are certain factors associated with an increased risk of herpes zoster? These results can be used to provide insights into the epidemiology of herpes

zoster, in particular regarding which patients in our clinical daily practice are at highest risk of disease. Furthermore, these findings may be used to inform policy makers in their assessment of the need for preventive strategies in the general population or whether such measures should be directed at certain persons who are at a high predicted risk of herpes zoster. The thesis also examines whether evidence supports that herpes zoster can be provoked by occult cancer because physicians need to know whether they should consider diagnostic testing for cancer when a patient presents with herpes zoster.

The thesis consists of nine chapters that follow the typical layout of a research paper. The background chapter provides an introduction to the definition, clinical manifestations, pathophysiology, treatment, and prevention of herpes zoster, followed by information on the state of the art regarding its occurrence and risk factors. Study IV, a systematic review of underlying cancer in patients with herpes zoster, is incorporated into this overview of the literature. Subsequent chapters describe methodology and results for studies I–III. Then follows a chapter in which results are put into the context of the literature review and methodological limitations. The last chapters include summaries in English and Danish and references. Full versions of the research papers are provided in the Appendix.

2. Background

2.1 Definition of herpes zoster

Herpes zoster, also known as shingles, is an infectious disease characterized by a vesicular rash and acute neuritis.[1] In most languages, the word for herpes zoster reflects the classic signs and/or symptoms.[1] Herpes is derived from the Greek work "herpein," which means "to spread" or "to creep." In Greek, the word zoster means "girdle," "belt," or "zone" and refers to a belt used mainly by men in Ancient Greece. "Shingles" stems from the medieval Latin word "cingulus," which has the same meaning. In some countries, terminology is influenced more heavily by the pain accompanying the acute neuritis in herpes zoster, *e.g.*, "hellfire" in Danish (helvedesild) or "belt of roses" in Swedish (bältros) and Dutch (gordelroos). In this thesis, herpes zoster is hereafter referred to simply as *zoster*.

2.2 Clinical presentation of herpes zoster

The terminology for zoster reflects the segmental distribution in which the painful rash spreads/creeps along a single body segment, most often on the trunk or face.[2] The afflicted area corresponds to the inflamed nerve, as demonstrated in an eminent series of autopsy studies published in 1900, where Head and Campbell mapped the anatomical distribution of zoster to the sensory neural pathways to the skin.[3] This work also formed the basis for the dermatome chart, which is well-known to most health professionals today.

The pain in zoster is typically described as a moderate to severe deep burning pain and often precedes the onset of the characteristic unilateral belt-like vesicular rash by 2 to 3 days.[2,4] In some patients, itch is more predominant than pain.[2,4] This prodromal phase may also be accompanied by general malaise, fever, and lymphadenitis. The development of the rash then begins with the gradual development of erythema and clusters of papules along the dermatome. The lesions progress sequentially through phases of vesicles, bullae, pustules, and crusting, with the different stages showing at the same time. In most people, the rash resolves within one month, potentially leaving pigment changes but little or no scarring.

Although zoster is seldom life-threatening by itself,[5] acute and chronic complications involving various organ systems can occur.[6] For example, dermatological dissemination and bacterial superinfection may lead to septicemia.[6] Visceral dissemination may cause inflammation of internal organs, *e.g.*, pneumonia, pericarditis, and hepatitis. Ocular complications, *e.g.*, stromal keratitis and acute retinal necrosis, may threaten sight. Furthermore, neurological complications can arise, including meningo-encephalitis, myelitis, vasculopathy, and paresis, *e.g.*, of the facial nerve (Ramsay Hunt syndrome). The most common complication of zoster is, however, post-herpetic neuralgia (PHN), which is defined as any pain persisting for 90 days or more after rash onset.[4] The risk of PHN after zoster is about 10%–30%,[4,5] increasing by 1.22–3.11-fold with each consecutive decade of age.[7] At least half of patients are refractory to available analgesics, and treatment satisfaction is low (15%).[4] PHN adversely affects quality of life and has been linked to depression, sleep disturbances, and loss of productivity and functional capacity.[4]

The diagnosis of zoster is often made clinically on the basis of its striking appearance. Differential diagnoses for the rash mainly include infection with herpes simplex virus, but painful acute medical conditions (*e.g.*, myocardial infarction, urolithiasis, or migraines) may be suspected in the prodromal phase or in the complete absence of a rash (*zoster sine herpete*). When necessary, laboratory confirmation with polymerase chain reaction analysis or viral culture of swabs from lesions, throat, or cerebrospinal fluid is helpful.[8]

2.3 The pathophysiology of herpes zoster

2.3.1 The varicella-zoster virus

Today, it is well-known that zoster is caused by the same virus that is responsible for the childhood exanthema varicella (chickenpox). However, it was not until 1909 when von Bókay linked the two conditions based on the observation that children often developed varicella after contact with persons suffering from zoster.[9] During the next half century, other researchers reported similar support of a connection between the two conditions. Kundratiz[10] and Bruusgaard[11] carried out experiments where varicella-susceptible children were inoculated with fluid from zoster vesicles, resulting in the development varicella and transmission to children without previous evidence of varicella. Abrahamson succeeded in protecting children from varicella during a hospital outbreak by administering plasma collected from a patient with recent zoster. Furthermore, laboratory studies using complement fixation tests and electron microscopy supported the similar nature of agents isolated from varicella and zoster.[12,13]

Despite this growing evidence, the common source of varicella and zoster remained controversial, with many scientists insisting on a distinction between ordinary and zoster-induced varicella. This conjecture was rejected by meticulous field studies where Hope-Simpson *et al.* showed that the incubation period for varicella (*i.e.*, the time from exposure to symptoms) was 14 days and transmission among all exposed persons was 60%, regardless of whether the outbreak was traced back to a case of varicella or zoster.[14] Furthermore, persons with a past history of varicella seemed immune in both types of outbreaks. The debate was finally resolved in the 1950s, when Weller and colleagues isolated identical virus in cell cultures from varicella and zoster.[15] To reflect its equal importance in both diseases, the virus was named the varicella-zoster virus (VZV). The virus is now classified in the International Committee on Taxonomy of Viruses as human herpesvirus 3, a DNA virus belonging to the alpha-subfamily of the herpesviridae.[8,16]

2.3.2 The natural history of herpes zoster

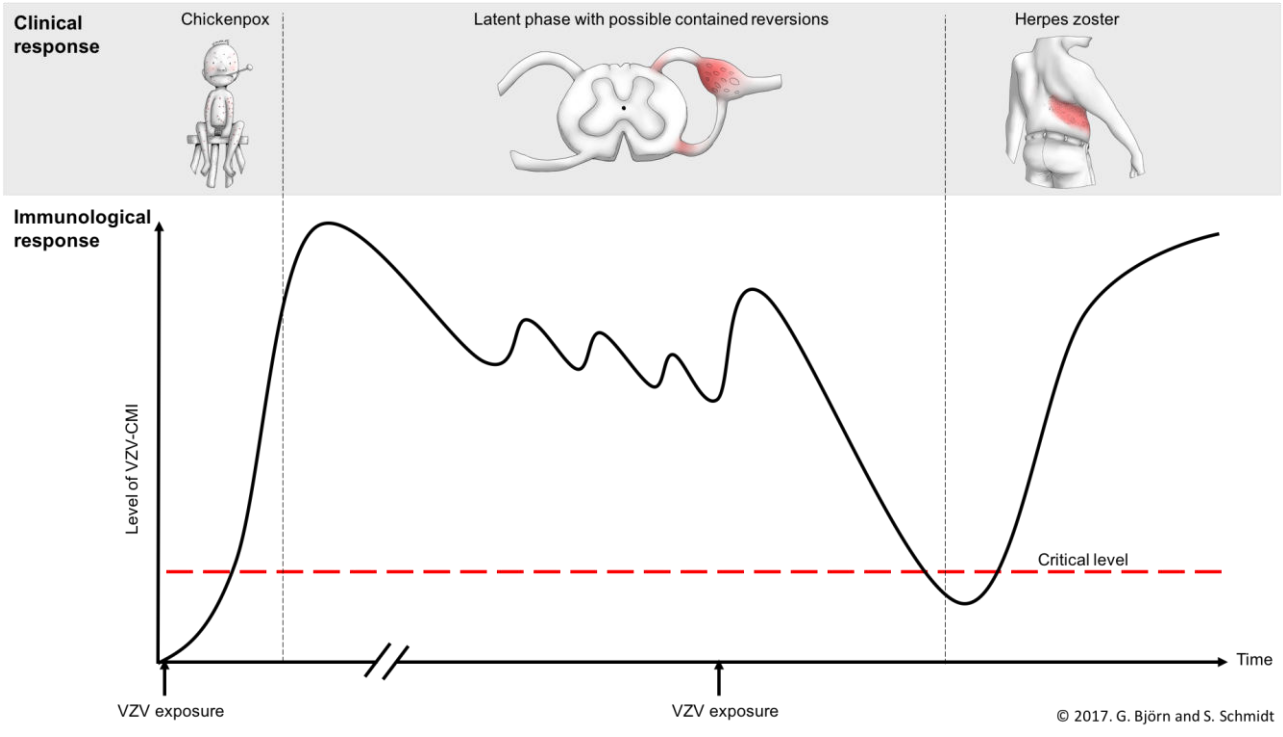
Despite identification of VZV, the pathophysiology of zoster remained unclear, and the scientific community was puzzled by the predominance of zoster in the elderly population and the lack of zoster epidemics. In 1965, Hope-Simpson proposed the progressive immunity hypothesis, which introduced the concepts of viral latency and natural immunity.[17] Figure 2 illustrates the clinical and immunological response divided into three phases: the primary infection (varicella), the latent phase, and reactivation (zoster).

The primary infection typically occurs in early childhood.[8] Varicella is usually mild and self-limiting, manifesting as a pruritic generalized rash with a centripetal distribution. Transmission is airborne from the vesicles of persons with varicella or zoster.[8] The incubation period is 10–21 days.[18] It is highly contagious, as 90% of susceptible household contacts contract the disease.[18] The contagious period begins 1 to 2 days before rash onset and continues until lesions have crusted.

During the primary infection, VZV infects sensory nerves through the blood stream or retrograde axonal transport from the skin.[8] In the convalescent period after varicella, the virus establishes latency in the sensory ganglia, marking the beginning of *the latent phase*. The exact mechanism of neuronal latency is unclear, but the dormant state typically continues for decades. During this period, subclinical reactivations (contained reversions) with increases in immunity may occur. Furthermore, exposure to VZV, *e.g.*, when taking care of a child with varicella, is thought to result in transient boosting of immunity. Although a humoral response is observed following the primary infection, the cell-mediated immunity (CMI) is the most critical component of adaptive immunity in terms of limiting reactivation.[19]

Reactivation occurs when the VZV-CMI decreases below a critical level, as shown by the arbitrary red horizontal line in Figure 2. Reactivation causes a lytic infection with ganglionitis and propagation of the virus along the sensory nerve to the skin, resulting in the clinical manifestations of zoster. The triggering drop in VZV-CMI may be related to an age-dependent decline in immunity (immunosenescence) or other risk factors (section 2.7).[8,20] Thus, although zoster primarily afflicts the elderly, pathophysiology begins in childhood when the majority of the population becomes VZV-seropositive.[21]

Figure 2. The clinical and immunological responses in the pathophysiology of herpes zoster. The y-axis of the graph shows the varicella zoster virus-specific cell-mediated immunity (VZV-CMI).



2.4 Treatment and prevention of herpes zoster

Because of the potentially severe complications of zoster, in particular the difficulties in managing PHN, efforts have been directed at identifying preventive strategies. This work has primarily centered around reducing the risk of reactivation through vaccination. A vaccine (Varivax®) of the live-attenuated Oka VZV strain has been available for over 20 years.[22] In Europe, Varivax is included in the childhood vaccination programs in six countries on a nationwide level (*e.g.*, Germany) and in two countries (Italy and Spain) at a regional level.[23] In the Shingles Prevention Study published in 2005, Oxman *et al.* found that use of a 14 times more potent formulation of Varivax can also reduce the incidence of zoster and PHN by 51% and 67%, respectively, compared with placebo.[24] The postulated mechanism behind this zoster vaccine (Zostavax®) was boosting of VZV-CMI, building on Hope-Simpson's original hypothesis of exogenous boosting. The immunogenicity, efficacy, and safety of Zostavax have been confirmed in subsequent studies.[24] In 2006, Zostavax was authorized in the US and Europe for use in adults aged 60 years or older (later adjusted to 50 years or older), making it the first vaccine approved for a latent infection. However, the vaccine price is high (approximately 190 Euro or 1400 Danish Krone),[25] and uncertainties exist with regard to long-term efficacy and need for boosters, safety in immune-incompetent persons, and burden of disease in most countries.[26] The World Health Organization (WHO) therefore offers no recommendations on routine immunization.[26] Most European countries have not implemented vaccination programs for Zostavax, and vaccine uptake has been limited in European and non-European countries that have done so.[27,28] However, a recombinant subunit vaccine (HZ/zu) has been tested in phase 1–3 clinical trials, showing an efficacy of about 90% with regards to preventing zoster for at least 4 years after vaccination.[24] With improved efficacy and safety compared with Zostavax in immune-incompetent patients, this vaccine holds great promise.[24]

Treatment of zoster is aimed at accelerating recovery, preventing complications, and alleviating pain.[29] The discovery of acyclovir in the late 1970s was a breakthrough in zoster treatment, gradually replacing previous treatment with the nonspecific cellular and viral inhibitor topical idoxuridine.[30-33] Today, mainstay therapy is a 7-day course with acyclovir (800 mg five times daily) or the newer valacyclovir (1000 mg three times daily) or famciclovir (250 or 500 mg three times daily, depending on country).[29] In some countries, brivudin is also licensed for use at a dose of 125 mg daily. These drugs are antiviral nucleoside (thymidine) analogues that, following phosphorylation in the human cell, actively inhibit the viral deoxyribonucleic acid (DNA) polymerases. This inhibition prevents further viral DNA synthesis and replication, leading to reduced time to cessation of viral shedding, formation of new lesions, and acute pain. The drugs are well-tolerated, as the pharmacodynamics are highly specific to the virus. Although the low cost of acyclovir has favored its use for many years, randomized controlled trials demonstrate superiority of valacyclovir and famciclovir.[29] Furthermore, these agents have better bioavailability and convenient dosing schedules. Valacyclovir, famciclovir, and brivudin have comparable efficacy.[29]

Antivirals are recommended for use in (i) immunosuppressed individuals, (ii) persons with complicated (*e.g.*, ophthalmic) zoster, and (iii) immune-competent persons who present within 72 hours after rash onset and fulfill one or more of the following criteria: age ≥50 years, moderate/severe pain,

moderate/severe rash, or non-truncal involvement.[29] In the absence of clinical and biological evidence, these criteria are based on inclusion criteria in antiviral trials. Other persons, *e.g.*, with ongoing vesicle formation despite late presentation, may also benefit from treatment.[29] Ocular involvement requires urgent referral to an ophthalmologist, who may initiate supplemental local treatment with cool/tepid compresses, topical steroids, mydriatic/cycloplegic agents, and/or ocular pressure–lowering drugs depending on severity and manifestations.[29] Systemic glucocorticoid (GC) treatment may be required in situations with severe ophthalmic or nervous system inflammation. Furthermore, depending on pain severity, comorbidity, and contraindications, scheduled treatment with regular painkillers (*e.g.*, acetaminophen), opioids, anticonvulsants and/or tricyclic antidepressants, or neural blockade may be necessary to alleviate acute herpetic neuralgia. Patients should be informed about the risk of transmission to VZV-susceptible persons.

2.5 Literature review

We performed two separate literature reviews for this thesis. First, we performed an online database search to identify studies reporting zoster rates (descriptive studies) and studies investigating risk factors for zoster (analytical studies). We searched MEDLINE (PubMed) on January 6, 2017, for studies indexed with the Major Medical Subject Headings (MeSH) topic "Herpes Zoster/epidemiology." We supplemented with a search of MEDLINE and EMBASE for studies with title terms 'zoster' or 'shingles' in combination with 'incidence', 'rate', 'risk', 'epidemiology', 'burden', 'trend', 'trends', 'association', or 'associated'. We did not consider studies limited to the pediatric population. To ensure comparability with rates reported in this thesis, we further restricted to descriptive studies that reported general population or hospital diagnosis rates of zoster in well-defined (nationwide or regional) source populations in Europe. Thus, we excluded studies restricted to selected patient populations (*e.g.*, dermatology clinics or trial populations). While the occurrence, or frequency, of disease can be measured in various ways (incidence, prevalence), we focused on incidence rates, *i.e.*, new cases of zoster per person-time at risk. Because differences in demographics of study populations or standard populations hamper direct comparison of crude or standardized rates, we selected studies that reported age-specific rates. For analytical studies, we required that reported data were sufficient for estimating the change in absolute and/or relative risk of zoster associated with the factor. We restricted to non-ecological designs and studies conducted in the general population, thus excluding risk factor studies in selected populations (*e.g.*, transplant patients). However, when appropriate, data falling outside this definition are discussed in the literature overview with reference to relevant studies and reviews.

Studies on the association between zoster and underlying cancer were identified in a separate search of MEDLINE and EMBASE, using variations of relevant indexing and free text terms for zoster, cancer, and risk (the search string is provided in Web Methods 3 of Paper IV). The last search date was February 18, 2016. We included studies of any design that reported absolute or relative effect measures for the association between zoster and risk of any cancer.

In both literature reviews, we followed the same procedure with database search, initial screening of titles and abstracts, retrieval of full-text papers where abstracts suggested that inclusion criteria were

satisfied, eligibility assessment, data extraction, and risk of bias assessment. We checked reference lists of retrieved full-text articles and relevant reviews to identify additional studies. We attempted to include non-English papers but excluded conference abstracts. When full-text papers could not be retrieved or when reported data were insufficient, we contacted authors for clarification. One author (myself) completed all steps of the literature review alone, except in the second review for cancer studies where a second author, blinded to my responses, repeated the eligibility assessment, data extraction, and risk of bias assessment.

The search for studies on zoster occurrence and risk factors yielded 1964 non-duplicate references in the electronic databases (1218 in PubMed and 1154 in EMBASE). We reviewed 175 full-text papers after initial screening of titles and abstracts and additionally 39 from reference lists. We were not able to retrieve full-text versions of six non-English studies, which were therefore excluded. Finally, we selected 18 studies on occurrence of zoster in the general population and/or the hospital-based setting in Europe and 97 studies assessing one or more potential risk factors for zoster. The flow chart for selection of the 46 studies for the systematic review on occult cancer in zoster is shown in Figure 1 in paper IV.

2.6 Occurrence of herpes zoster

2.6.1 The general population

Studies reporting age-specific incidence rates of zoster in the general population are described in Table 1.[34-43] Studies were based on data collected through sentinel surveillance networks (*i.e.*, active data collection on one or more conditions in a selected population sample),[44] administrative or research databases, or observational studies. Most had individual-level data on incident diagnoses, but some counted episodes, which may include recurrences or repeated contacts for complications.[36,42]

In Figure 3a, the age-specific rates from the studies are plotted against the midpoint of each age group. Although zoster is a mandatory reportable disease in Slovenia,[43] data from this country are clearly incomplete. In the remaining studies, there is a steep increase in the rate of zoster with age from about 2 to 4 per 1000 person-years at age 40 years to 5.6 to 15 per 1000 person-years at above age 90 years. Zoster is thus a common disease, in particular among the elderly. Hope-Simpson estimated that up to 50% of persons living until 85 years of age would experience zoster.[17] The marked increase with age is thought to stem from aging of the immune system (immunosenescence)[45] and may also be related to cumulative exposure to risk factors, *e.g.*, chronic diseases and immune-modulatory treatments. Most studies also support a 13%–56% higher rate of zoster among women, particularly after age 44 years.[46] Reasons for this difference are unclear.

Previous reviews conclude that rates of zoster are similar across Europe, North America, Australia, and Asia.[5,46] Nevertheless, Figure 3a indicates some variation when considering age-specific rates, especially for the oldest age groups. This finding may be explained by lack of precision or underascertainment among frail elderly (decreased detection and/or registration) in some settings. Although we aimed at including the most recent data from each country, comparison of rates from different calendar periods can also create an impression of differences, as zoster rates seem to be increasing globally.[5]

Overall, the literature review shows that data on the occurrence of zoster in the general population in Europe are sparse, as most countries do not record cases of zoster routinely.[22,23] Denmark is no exception, and few studies thus have examined the occurrence of zoster in detail. In 1985, Christensen and Nørrelund conducted a study among 395 randomly selected general practices (10% nationwide sample), of which 276 agreed to collect data on patients presenting with zoster during a 3-month period.[47] Authors estimated that rates of zoster increased from approximately 1 per 1000 person-years at age 40 years to 5.5 per 1000 person-years among those aged 90 years. Although temporal changes[5] may explain why these estimates are lower in Figure 3a, they are also below that found by Hope-Simpson in 1965.[17] Methodological limitations should therefore be considered, including underreporting from participating practices. Furthermore, while zoster patients with immune incompetence (malignant disease, GC treatment, or use of other immunosuppressants) were excluded, they seem to have been included in denominators for rates, which may have resulted in underestimates. Another author reported a crude rate of 2.5 per 1000 person-years in a general practice in North Zeeland during 1909–1943, but age-specific rates were not available.[48]

In a more recent Danish study from 2009, the prevalence of zoster was estimated through telephone interviews with 1207 individuals aged 50 years or older.[49] In total, 166 patients (14%) reported a history of zoster. Incidence rates were not estimated, and interpretation of findings is complicated by the small study sample, potential recall bias, and selection bias, as participants were randomly chosen from a database of 200,000 individuals recruited through influenza vaccination campaigns.

2.6.2 The hospital-based setting

Herpes zoster is sometimes diagnosed and treated in the hospital sector during admission or in the outpatient clinic (ambulatory) setting. Admission is mainly indicated for persons with complications or to avoid progression in individuals at high risk of viral dissemination (*e.g.*, transplant patients).[29] Although hospital contact overall is rare, a significant proportion of expenditures related to zoster is attributed to hospital costs.[50] A complete picture of the spectrum of disease and burden of zoster thus also entails an assessment of occurrence in the hospital-based setting.

European studies reporting age-specific rates of hospitalizations with zoster listed as a diagnosis are described in Table 1.[38,40,51-58] The rate increases with age but varies largely between countries (Figure 3b and 3c). Hospitalization rates may be particularly sensitive to a country's healthcare structure. Indeed, in a previous study, we provided a description of zoster patients diagnosed at Danish hospitals and found that length of stay and distribution of complications were close to that observed in Sweden but only half of that observed in Southern Europe.[59] At the same time, hospitalization rates were similar or lower in Southern Europe (Figure 3b and 3c), suggesting that milder cases of zoster are hospitalized in Denmark and Sweden. Extrapolation between countries may therefore be inaccurate when assessing the burden of zoster in the hospital sector. Rates of zoster in hospital outpatient clinics specifically have not been reported in other European countries but may constitute a different group of patients, *e.g.*, cancer patients attending regular check-ups and patients referred to ophthalmologist clinics for acute assessment.[59]

Table 1. European studies reporting age-specific rates of zoster, by setting and country

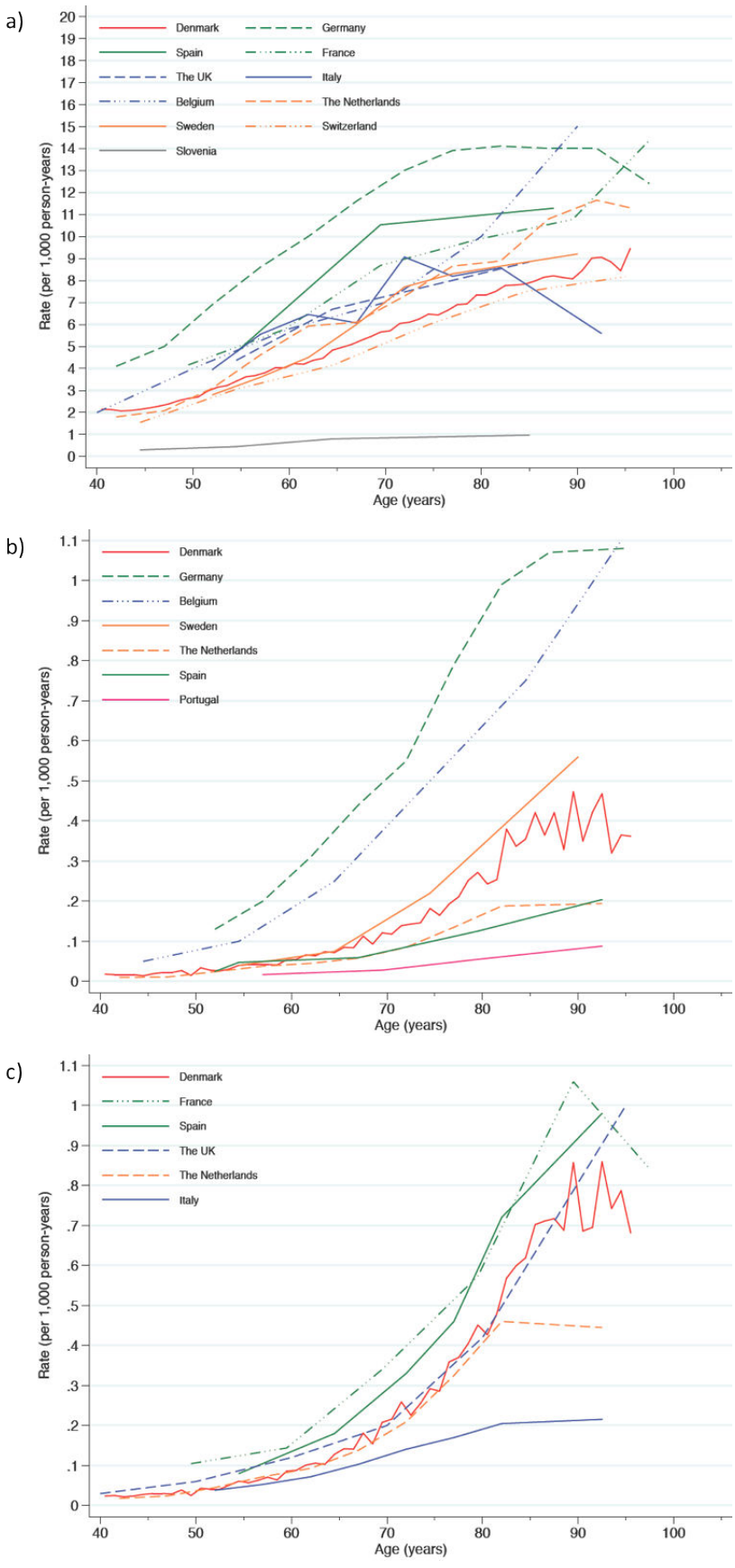
Country	Setting	Data source (period)	Case ascertainment
General population			
Sweden[34]	Västra Götaland County	The Västra Götaland County Primary Health Care Registry and the Swedish Patient Registry (2008–2010)	ICD-10 codes, both primary care and hospital (in- and outpatient) diagnosis
Denmark (thesis paper I)	Nationwide	The Danish National Prescription and Hospital Registries (1997–2013)	Antiviral prescriptions or ICD-10 codes, entire healthcare sector
The UK[35]	>600 GPs	CPRD (2010)	Read codes
Germany[36]	3 statutory health insurances across Germany	The German Pharmacoepidemiological Research Database (2005–2009)	ICD-10 codes, both primary care and inpatient primary diagnosis
The Netherlands[37]	~150 GPs	The Netherlands Institute of Primary Health Care sentinel surveillance network (2002–2011)	ICPC codes
Belgium[38]	150 GPs	The sentinel system of the Scientific Institute of Public Health (2006–2008)	Notified by physicians
Switzerland[39]	250 GPs, pediatricians, and internists	The Sentinella voluntary reporting network (1998–2001)	Notified by physicians
France[40]	1200 GPs	Sentinelles surveillance general practitioners network (2005–2008)	Notified by physicians
Italy[41]	56 GPs from Liguria, Puglia, Toscana, and Veneto regions	Observational study (2013–2015)	Diagnosis or antiviral prescription for zoster in GP records
Spain[42]	Madrid	Electronic clinical records in primary care (2005–2012*)	ICPC codes and associated free text
Slovenia[43]	Nationwide	National surveillance data for notifiable communicable diseases (1996–2005)	ICD-10 codes, entire healthcare sector
Hospital sector			
Sweden[51]	Nationwide	Swedish National Patient Register (2006–2010)	ICD-10 codes, In (A)
Denmark (thesis paper I)	Nationwide	The Danish National Hospital Registry (1997–2013)	ICD-10 codes, In/Out/ER (A, A+B)
England[52]	Nationwide	Hospital Episode Statistics (Apr 1, 2004–Mar 31, 2013)	ICD-10 codes, In (A+B)
Germany[53]	Nationwide	Federal Health Monitoring System for inpatient and mortality data (2007–2008)	ICD-10 codes and 'assured'/'suspected' reliability listed, In (A)
The Netherlands[54]	Nationwide	The Prismant National Health Care Registry (1994–2001)	ICD-9 and ICD-10 codes, In (A, A+B)
Belgium[38]	Nationwide	Hospital Minimal Clinical Data (2000–2007)	ICD-9 codes, In (A)
France[40]	Nationwide short-stay/acute-care hospitals	The PMSI Data processing center for hospital discharges (2000–2006)	ICD-10 codes, In (A+B)
Italy[55]	Veneto, Toscana, Lazio and Campania regions	National hospital discharge records (2003–2005)	ICD-9 codes, In (A+B)
Spain[56,57]	Nationwide	MBDS (2005–2010*)	ICD-9 codes, In (A+B)
	Madrid	MBDS (2003–2013)	ICD-9 codes, In (A) of >1 day
Portugal[58]	Almost entire mainland Portugal	Portuguese Ministry of Health database for hospital admissions (2000–2010)	ICD-9 codes, In (A)

Abbreviations: A=primary diagnosis; B=secondary diagnosis; CPRD=Clinical Practice Research Datalink; ER=emergency room contact; GP=general practitioner; ICD=International Classification of Diseases; ICPC=International Classification of Primary Care; In=Inpatient contact; MBDS=the Minimum Basic Dataset; UK=United Kingdom; Out=Outpatient contact; PMSI=Programme de Médicalisation des Systèmes d'Information.

*Only the last year in the study period was used to compute age-specific rates.

Note: When one or more studies reported age-specific rates from the same country/region, we selected the most comprehensive or recent report. Thus, the 18 studies in the table were selected from a total of 44 studies reporting on age-specific rates of zoster.

Figure 3. Age-specific rates of zoster in the general population (a), of admissions with zoster as primary diagnosis (b), or of admissions with zoster as either primary or secondary diagnosis (c) in Europe. Note different scales of the y-axes



2.7 Risk factors for herpes zoster

2.7.1 Sociodemographic and lifestyle factors

Table 2 offers an overview of evidence pertaining to sociodemographic and lifestyle factors as determinants of zoster. References are given in the table. Increasing age and female sex are probably the most widely studied risk factors for zoster and have been described in section 2.6.1. Several other sociodemographic determinants have also been examined. *Genetic susceptibility* is important, as suggested by studies linking zoster to a positive family history and certain gene variants, as well as differences in the occurrence of zoster by *race or ethnicity* (less common in non-whites).

Periodic boosting of VZV-CMI because of increased *VZV exposure* has also been hypothesized as an explanation for ethnic differences, as well as several other sociodemographic factors. Direct evidence for a clinically relevant effect of exogenous boosting is sparse, as only three case–control studies have examined the association between zoster and self-reported varicella contacts. Unfortunately, studies were inconclusive because they included small numbers of participants and considered different exposure windows (one month, one year, or 10 years before zoster). Furthermore, two of the studies were conducted in the United States (US) after implementation of universal varicella vaccination, resulting in low exposure prevalence. Two other case–control studies found an inverse dose-response relationship between number of contacts to children and relative risk of zoster, which seemed to be at least partly mediated by varicella exposure based on data collected in one study.[60] Immunological studies also support an effect, but data on duration of boosting are sparse.[61] An immediate protective effect is contradicted by lack of reciprocal *seasonality* patterns for zoster and varicella in most studies. Furthermore, although mathematical models have forecasted an increased incidence of zoster after implementation of universal varicella vaccination,[61] current evidence suggests that reduction in exogenous boosting does not entirely explain *secular trends* in rates.

As high population density and crowding may increase exposure to VZV, low *socioeconomic status* and rural *residence* have also been proposed as predictors of zoster. However, data are conflicting, and differences in healthcare access, health-seeking behavior, lifestyle, and exposure to environmental immunotoxic agents complicate the picture. Such factors are also likely to depend on country, which further hampers comparison and interpretation of studies.

Although several aspects of *lifestyle* (*e.g.*, tobacco[62] and alcohol consumption[63]) may have adverse effects on CMI, few epidemiological studies report data on the association between health-related behaviors and zoster. Overall, previous studies show no association between zoster and smoking, alcohol consumption, body mass index, or physical exercise, but a potential protective effect of high micronutrient intake was reported in one study. As most previous studies have been designed with other aims, dose-response analyses are lacking, which limits interpretation about causality.

Table 2. Evidence for sociodemographic and lifestyle factors as potential risk factors for zoster

Risk factor	Epidemiological evidence*	Proposed hypotheses
Age	- Rates of zoster increase with increasing age (Figure 3).	- VZV-CMI declines with age,[20,64-68] most likely due to immunosenescence or accumulation of immunosuppressive factors.
Sex	- Women are more frequently diagnosed with zoster, with some studies suggesting the difference is evident mainly at age ≥45 y (reviewed in [46,60]).	- Women seek healthcare for zoster more often and earlier.[69] - Sparse data on sex-differences in VZV-CMI.[70,71] Could hypothetically be explained by higher prevalence of autoimmune diseases,[72] hormonal fluctuations,[73] or genetics. - Paradox assuming women have more frequent contact with children (see 'VZV exposure'), although that may explain lower sex differences in persons <45 y.[60,69,74]
Genetic susceptibility	- Five CC studies using self-reported data give ORs of 1.87 to 4.91 for family history of zoster in a first-degree relative among zoster cases vs. controls.[69,75-78] - Two of the studies found similar ORs for first- and second-degree relatives[69,75] whereas one study found an OR of 0.81 for non-first-degree relatives (1.87 for first-degree).[78] - Four studies examined if the association depended on number of relatives with positive family history and found higher ORs for multiple than for single relatives.[69,75,76,78]	- Persons with zoster have higher or lower frequency of certain gene variants that may be implicated in viral productivity and CMI, including genes for interleukin-10 (possibly depending on ethnicity),[79,80] major histocompatibility complex proteins,[81,82] apolipoprotein A (in women),[83] and mitochondrial function.[84]
Race/ethnicity	- Six studies reported between 0.29 and 0.69 times lower risk of zoster in non-white (black and/or Hispanic) *vs.* white people.[60,85-89] - One cohort study reported an IRR of 0.94 (0.90–0.99) for dark *vs.* fair skin color, which may be explained by racial differences.[90]	- Genetic differences in susceptibility to infections.[91] - Selection of immunologically resistant elderly in ethnic groups with high mortality. - Closer contact with children (see 'VZV exposure'); however, adjustment for current household contacts had no effect in one study.[60] - Difference in age at varicella (see below), although one study adjusted for birth country.[60] - Different prevalence of zoster risk factors, but RRs persist in multivariable models.[87-89] - Ease of diagnosis may depend on skin color.[90]
Age at varicella	- Country of origin often used as proxy, as varicella generally presents later in tropics.[60] - An Australian cohort study found no association between being Australian-born and risk of zoster (IRR 1.00; 0.95–1.06)[90] while a Spanish study found that risk of zoster was lower in people from other (temperate or tropical) countries (IRRs from 0.38 to 0.71)[92] - A UK cohort study reported lower RR in persons born in tropical countries (0.64; 0.30–1.20), especially countries with strong evidence of late-onset varicella (0.56; 0.28–1.12).[60]	- Late onset of varicella translates into a corresponding delay in onset of zoster.
VZV exposure	- One cross-sectional survey found that varicella exposure in the past year was more common among zoster cases than controls[85] whereas two CC studies found no association with contacts in the past 10 y[93]or past month.[77] However, studies were small, and two were conducted in settings with universal varicella vaccination.[85,93] - Two CC studies on contacts with children in the past 10 y (as proxy for varicella contacts) found inverse dose-response relationships with ORs <0.5 in most heavily exposed.[94,95] Similarly, three studies found a protective effect of living with a child currently or in the past 10 y.[74,77,96] One study found no association with having children.[90] - Studies using profession as proxy for frequent (childcare workers[60] or certain health professionals[97,98]) or rare (members of isolated monasteries[99]) contacts are conflicting. - Ecological data conflicting (see 'secular trends' and 'seasonality')	- Hope-Simpson's exogenous boosting hypothesis suggests that re-exposure will boost VZV-CMI.[17] Proof of concept is provided by some immunological studies (reviewed in[61]) and the Shingles Prevention Trial.[20] - VZV-exposure assumed to be lower upon contact with a zoster patient due to lower transmission potential
Secular trends	- Global increase in rates of zoster, both in countries with and without national varicella	- Increased longevity and use of immunosuppressants.

	immunization, and starting even before implementation in the former.[5]	- Increased public awareness, access to healthcare, and improved recording. - Reduced exogenous boosting in countries with universal varicella vaccination.
Seasonality	- Most large studies do not support seasonality (reviewed in[60]), but ecological data are conflicting on the correlation with varicella incidence and UVR levels.[100-103] - One study found no association between hours spent outdoors and zoster.[90]	- Higher incidence in summer due to immunosuppression from UVR.[104] - Decreased rates during periods with varicella outbreaks due to exogenous boosting.
SES	- Various measures of high SES (*e.g.*, high education, low deprivation level of residence, high income) have been associated with increased risk of zoster,[85-87,92,95,105] although three cohort studies from UK, Australia, and US found no association.[60,89,90] Findings are difficult to interpret based on diverse healthcare systems and risk of self-selection bias particularly in CS and CC studies.[85,86,95] - Two studies reported increased RRs associated with measures for health-seeking (outpatient visits in past year,[88] use of supplements,[90] use of preventive health screening[90]). - Three studies reported increased RRs (1.08 to 1.17) for persons in a relationship *vs.* singles,[60,89,90] but one of the studies also found no association with good social support.[89]	- SES affects health behaviors, which may increase risk of zoster directly (see 'lifestyle') or through chronic diseases. - High SES may increase healthcare-seeking, working in the opposite direction. - Population/household crowding and probability of VZV exposure may vary by SES.
Residence	- Two studies from UK[60] and US[106] found no increased RR of zoster in persons with rural *vs.* urban residence, but an Australian study found higher risk for residence in major city.[90] - Other studies compared various regions in Taiwan,[98] Israel,[107] and the US,[85] but interpretation is difficult because of mixed urban and rural districts in the areas. - One study suggested that exposure to immunotoxic chemicals, measured indirectly by residence (and directly by self-report), was associated with risk of zoster, mainly in younger residents.[108] Another CC study found no association with self-reported pesticide exposure.[78]	- Crowding in areas with high population density may result in lower risk through exogenous boosting. - Differences in immunosuppressive environmental factors, *e.g.*, certain chemicals.[109] - Differences in proximity to physician.
Lifestyle	- Data on smoking and zoster are perplexing,[35,49,60,77,78,86,89,90,95,110] as several studies show that RR is decreased in current smokers and increased in former smokers.[35,49,86,90] Possibly biased by smoking cessation after diagnosis of, *e.g.*, cancer. - Studies on alcohol consumption,[35,77,86,90,95,110] BMI,[35,77,90] and physical exercise[90] are sparse and conflicting, generally showing no association. - One CC study found an inverse dose-response relationship between zoster and self-reported intake of micronutrients.[111] No difference in odds of fair/poor self-rated diet or median intake of vegetables and fruit in another CC study.[78] - Except for one CC study on micronutrient intake, dose-response analyses are lacking.	- Cigarette smoke,[62] alcohol,[63] and unhealthy diet (in particular, insufficient micronutrient intake[112]) may cause reduced CMI. - Although underweight may be linked to malnutrition, obesity is also characterized by low-grade, chronic inflammation with possible functional immune deficiency.[113] - Exercise may influence immunity through hemodynamic and endocrine changes, but associations are complex and possibly U-shaped, as decreased T-cell function has been observed in athletes during periods with intensified training.[114]

Abbreviations: BMI=body mass index; CC=case–control; CMI=cell-mediated immunity; CS=cross-sectional; IRR=incidence rate ratio; OR=odds ratio; RR=relative risk measures, incl. IRRs, risk ratios, PR, ORs and HRs; SES=socioeconomic status; UK=United Kingdom; US=United States; UVR=ultraviolet radiation; VZV=varicella-zoster virus; y=year/years.
*Fully adjusted study estimates were selected. When estimates from single studies are shown, precision is measured using 95% CIs unless otherwise stated.

2.7.2 Somatic diseases and treatments

Table 3 summarizes the most common somatic conditions and treatments examined as risk factors for zoster, either as primary exposures of interest or covariates. *Systemic immunosuppressants*, *transplantation*, *human immunodeficiency virus (HIV)*, *other immunosuppressive diseases*, and *cancer* are associated with increased risk of zoster. However, absolute or relative increases in risks associated with these conditions in the general population are unclear, as few studies included comparison groups. Various *autoimmune diseases of the skin or connective tissue* have also been linked to increased susceptibility to VZV reactivation. Rheumatoid arthritis (RA) and subacute or systemic lupus erythematosus (SLE) have been studied most. Although immunosuppressive treatment plays an important role, disease pathogenesis may contribute. An increased risk of zoster is also reported for *inflammatory bowel disease* (IBD) in several studies. Data on other autoimmune diseases are sparse. Multiple sclerosis was linked to increased risk of zoster in two studies.[100,115] One hypothesis-generating study[116] and a cross-sectional study[117] found increased ORs for hypothyroidism, which in many cases has autoimmune etiology.

Seven of eight epidemiological studies support an increased risk of zoster in *asthma* patients. Potential associations have also been noted for other atopic diseases (allergic rhinitis[86,116,118] and atopic dermatitis[86]) and food allergy.[86] Five large studies based on routinely collected healthcare data also found that *chronic obstructive pulmonary disease* (COPD) was a possible risk factor for zoster, but smaller case–control studies with self-reported data on COPD are more conflicting. These associations may be caused by use of oral GCs,[35] but it is unclear whether the limited systemic absorption of inhaled GC plays a role.

An increased zoster risk is reported for non-malignant *kidney disease*, possibly explained by immune dysregulation due to accumulation of metabolic waste or vitamin D deficiency. Large differences in estimates from previous studies may result from differences in disease severity, adjustment for immunosuppressants, or risks of bias. Chronic kidney disease (CKD) may also link *diabetes* to zoster, but immune dysregulation could also play a role, especially for type I diabetes, which has a clear autoimmune component. Unfortunately, most previous studies failed to differentiate between types of diabetes.

A plethora of other possible risk factors have been examined. Studies consistently report increased risk after trauma.[77,78,86,119-121] Coronary artery disease has been linked to a 17%–24% increased relative risk,[86,92,116] but associations may be confounded by hypercholesterolemia[49,116] and statins.[122-125] Results are conflicting for other heart and cerebrovascular diseases.[49,77,86,88,90,92,95,116,126,127] One or two studies each detected increased risks for non-atopic skin diseases,[86] other infections,[100] tonsillectomy,[78] cirrhosis,[86,128] hypercalcemia,[129] peptic ulcers,[77,130] headache,[77] osteoarthritis,[77,116] osteoporosis,[77] gout,[116,131] balanitis,[132] prostatectomy,[133] dyshidrosis,[134] and sleep disorders.[78,135] Hypotheses for these studies are generally unclear, and most were small single-center cross-sectional studies[129,136] or case–control studies relying on volunteers and valid self-reports.[77,78,86] The registry-based Taiwanese studies[128,130,132-135] can also be challenged methodologically, as matched controls or unexposed cohorts were selected by conditioning on information attained after the index date. This process may have caused selection of, *e.g.*, disproportionally healthy comparators or persons who were unexposed simply due to death from causes that could be linked to zoster.

Table 3. Evidence for various non-psychiatric diseases and treatments as potential risk factors for zoster

Risk factor	Epidemiological evidence*	Proposed hypotheses
Systemic immuno-suppressants	- In studies conducted in the general population, the RR of zoster is increased by 1.33 to 2.06 for users of systemic GC,[35,77,100,107] 1.46 to 4.52 for users of other immunosuppressants and antineoplastic drugs,[35,107] and 2.21 to 2.73 for users of biologicals,[100,105] compared with persons not treated with these agents recently or ever. - Exposure definitions (*e.g.*, time frames and drugs), age groups, and adjustment factors vary. - Studies also report increased RR of zoster (1.72 to 3.43) in persons classified as immune incompetent, typically incl. immunosuppressive drugs, HIV, and cancers in the definition.[87,90,137] - In studies of persons with autoimmune diseases (see below), various immunosuppressive drugs have also been associated with increased risk of zoster.[138,139]	- Given intended effects on the immune system, immunosuppressive drugs increase the risk of infection, *e.g.*, systemic GC results in reduced synthesis of inflammatory cytokines, function of antigen-presenting cells, and T-cell activation.[140,141]
Transplantation	- Studies in the GP estimate RRs of zoster of 1.03 (0.26–4.12)[105] and 5.89 (0.12–292.36)[86] after any transplantation, 8.9[115] and 13.71 (2.73–68.94)[35] after HSCT, 3.5 after any SOT,[115] and 4.61 (4.13–5.14) after liver transplantation specifically.[142] Estimates are very imprecise. - Studies without comparison cohorts report rates higher than in GP outside the studies.[142-146]	- Transplantation requires chronic immunosuppressant treatment, which reduces CMI. Given different doses/types of immunosuppressants needed, risk is presumed highest after HSCT followed by lung and heart transplantation.[142]
HIV	- Studies based in the GP consistently report increased RRs of 1.53 to 5.07 among HIV+ vs. HIV– patients.[35,92,100,105,107,115,147,148] One small CC study reported an OR of 1 (0.09–11.0).[77] - Even higher RRs (up to 15) reported in pre-HAART era[148] and in populations without ready access to treatment[149] Very high estimates are also reported for zoster as a marker of undiagnosed HIV[150,151] and selected high-risk groups (*e.g.*, men who have sex with men[152,153]).	- HIV infects CD4+ T-cells, macrophages, and dendritic cells, resulting in progressively low levels of CD4+ T cells with broad impairment of CMI and risk of opportunistic infections.[154]
Other immunosuppressive disease	- Other diseases with immunodeficiency were associated with an IRR of 1.65 (1.50–1.80) in a Spanish cohort study[92] and an OR of 1.49 (1.05–2.12) in a UK CC study.[35]	- Similar to HIV, diseases with defect CMI, *e.g.*, DiGeorge syndrome, are thought to result in impaired VZV-CMI, while anecdotal reports suggest this is not the case for isolated humeral defects (*e.g.*, agammaglobulinemia).[19]
Cancer	- 16 studies report increased RRs of zoster in cancer.[35,49,77,86,90,92,98,100,105,107,110,115,126,147,155,156] Only two studies found no increase in RR for any cancer but may have been affected by selection bias for this association (*e.g.*, by excluding immune-incompetent patients).[89,95] - Estimates are generally not comparable, as time since cancer diagnosis and cancer subtypes vary in the studies. Nevertheless, stronger associations are consistently reported for hematological cancers[35,86,107,126,147,155,156] than for solid cancers.[126,147,155,156]	- CMI may be reduced in patients with cancer due to carcinogenesis itself or radio/chemotherapy. VZV-CMI in particular has mainly been examined in hematological cancer, showing decreased levels both at diagnosis and after initiation of therapy.[157-160]
Autoimmune skin or CTD	- Increased but highly varying RR of zoster estimates have been reported for patients with any autoimmune disease (1.26 to 3.04),[77,86,98,100] RA (1.13 to 2.54),[35,87,115,121,126,131,161,162] and SLE (1.29 to 4.11),[35,115,126,131,147,163-166] with two small negative studies (0.67[77] and 1.0[167]) on RA. - Lowest estimates are reported in studies with prospectively collected data and adjustment for immunosuppressive treatments, which seem to explain at least part of the risk.[35,87,161-164,167,168] However, disease severity may also predict zoster.[162,163,167] - 1 or 2 studies each have also found increased RRs (between 1.22 to 4.77) for Sjögren's syndrome,[126,168] giant cell arteritis,[169] ankylosing spondylitis,[131] dermatomysositis,[170,171] psoriasis,[115,131] alopecia areata,[172] cutaneous lupus,[171] pemphigus vulgaris,[171] and bullous pemphigoid,[171] but without adjustment for important confounders, incl. age and sex.[171] - Studies without comparison cohorts also show higher rates than in GPs outside the studies.[138,173]	- Patients with autoimmune diseases have a dysregulated immune system because of disease pathogenesis and immune-modulatory treatments (see 'systemic immunosuppressants').[72] - Specifically, correlates of VZV-CMI are reduced in patients with SLE, with conflicting findings regarding the role of immunosuppressants.[174-177] - Effectiveness of Zostavax may decrease faster in patients with autoimmune diseases.[178]

IBD	- 7 studies reported RR for zoster of between 1.21 and 2.42,[35,87,115,131,179-181] with estimates of 1.21 to 1.28 in studies adjusting for immunosuppressants.[35,87] - Unclear if the association may be stronger for Crohn's disease[179,180] or ulcerative colitis.[181] - Systemic immunosuppressants identified as at least partial mediators of risk.[35,87,179,180]	- As an autoimmune disease, IBD is characterized by immune dysregulation.[72] - Second- and third-line therapies for IBD are systemic immunosuppressants.[182]
Asthma	- An increased RR of zoster of 1.11 to 1.48 in asthma patients,[35,77,86,90,92,100,183] except in one small CC study that found an OR for self-reported asthma of 0.78.[77]	- Asthma is characterized by predominance of Th2-cells and suppression of Th1-cells.[184] This immune dysregulation may increase risk of viral infections, but treatment could also play a role (see 'inhaled GCs').
COPD	- Five studies using routinely collected data found RRs of zoster between 1.17 and 1.68 among COPD patients.[35,87,92,116,185] - Three CC studies using self-reported data are more conflicting.[77,86,95] - 'Lung disease' was associated with zoster in a claims database study of unvaccinated persons (HR 1.34),[88] whereas a smaller cross-sectional study found no association (OR 0.90).[49]	- COPD is associated with local and systemic dysregulation of the CMI,[186,187] and some have suggested that COPD should be regarded an autoimmune disease (triggered by smoking) extending beyond the lungs,[188] placing it in the same category as, *e.g.*, RA. - GCs may reduce CMI (see 'systemic immunosuppressants' and 'inhaled GCs').
Inhaled GCs	- A CC study using CPRD data found an association between inhaled GC and zoster (aOR=1.13; 99% CI 1.08–1.17) after adjusting for numerous risk factors, incl. asthma and COPD.[35] - Another CPRD study found an OR of 1.00 (0.94–1.07) for inhaled GC among regular users of respiratory drugs.[189] There was no variation by dose or cumulative use, but a potential association was found for high-dose use in combination with CYP3A4-inhibitors (OR 1.23, 0.81–1.88).	- Although bioavailability is limited, inhaled GCs may be absorbed through the airways and cause adverse effects similar to at least low-dose systemic GCs ('see systemic immunosuppressants').[190-193] - Interaction with drugs metabolized via CYP3A4 may increase adverse effects of inhaled GCs.[194]
Kidney disease	- RR of zoster between 1.22 and 2.21 in persons with kidney disease in all except one study (HR 1.04).[35,86,87,98,126,195-197] - Highest estimates reported in studies of AKI, 'uremia', or 'renal failure' (1.71 to 2.21),[98,126,195,196] while weaker associations (1.12 to 1.60) are reported for studies incl. codes for early-stage disease.[35,87] Studies reporting high estimates also tended to have high risk of bias due to, *e.g.*, use of inappropriate comparison cohorts.[126,195,197]	- Uremia in end-stage renal disease or acute kidney failure results in immune dysfunction, *e.g.*, impaired activation of T-cells, as demonstrated by increased rate of various infections, impaired vaccine response, and reduced skin hypersensitivity.[198] Pharmacotherapies, dialysis, and protein energy-wasting may also contribute,[198] as may vitamin D deficiency.[199]
Diabetes	- In studies using prospectively collected data, the RR for zoster associated with diabetes varies largely between 1.02 and 2.38,[35,87,90,92,105,107,116,126,131,147,200-202] even in studies reporting analyses from the same data sources.[87,116,131,147,201,202] One study found a decreased OR (0.87) for diabetes but may have been biased for this association, which was not the main focus of the paper.[121] Nevertheless, the lowest RRs are generally found in studies with low risk of residual confounding. - Few studies distinguished between type I and type II diabetes, reporting conflicting results,[35,100,203,204] and misclassification of type may have occurred (*e.g.*, there were many children with type II diabetes in one study[204]). - Studies using self-report or cross-sectional assessment of any diabetes in zoster patients and controls are even more conflicting reporting ORs and PRs between 0.51 and 3.3.[49,77,86,95,110,205-207]	- Patients with diabetes have dysregulated CMI related to pathogenesis of the disease.[208] Furthermore, one study found decreased VZV immunity specifically in diabetes patients.[209] - Poor glycemic control may also affect adaptive immunity.[208] - Some antidiabetic drugs may have anti-inflammatory properties.[210] - Neuronal stress due to microvascular disease may provoke reactivation.[211] - Diabetic nephropathy may increase risk of zoster (see 'Kidney disease'). - Although an autoimmune component has been recognized in type II diabetes in recent years, the pathogenesis of type I and II diabetes has been found to be distinct, and they should thus be separated if possible.[212]

Abbreviations: AKI=acute kidney injury; CC=case–control; CKD=chronic kidney disease; CMI=cell-mediated immunity; COPD=chronic obstructive pulmonary disease; CTD=connective tissue disease; CYP3A4=cytochrome P450 3A4; GC=glucocorticoid; GP=general population; HAART=highly active antiretroviral therapy; HIV=human immunodeficiency virus; HR=hazard ratio; HSCT=hematopoietic stem cell transplantation; IBD=inflammatory bowel disease; incl.=including; IRR=incidence rate ratio; OR=odds ratio; PR=prevalence ratio; RA=rheumatoid arthritis; RR=relative risk measures, incl. HRs, IRRs, risk ratios, PRs, and ORs; SLE=subacute/systemic lupus erythematosus; SOT=solid organ transplantation; UK=United Kingdom; VZV=varicella-zoster virus.
*Fully adjusted study estimates were selected. When estimates from single studies are shown, precision is measured using 95% CIs unless otherwise stated.

2.7.3 Psychological stress and mood disorders

It is commonly thought that psychological stress increases the risk of infections.[213] Psychological stress results when an event or demand exceeds an individual's ability to cope.[213,214] The body attempts to overcome this stress and maintain homeostasis through a process termed allostasis.[214] However, severe, recurrent, and/or chronic stress may overload the allostatic systems and result in negative physiological reactions, including suppression of the immune system. While studies of laboratory-induced hyperacute stress suggest an initial beneficial immune activation, a decrease in circulating counts and activity of cytotoxic lymphocytes is observed after exposure to more acute/chronic naturally occurring stressors.[215] This stress-induced immunosuppression is mainly mediated through hyperarousal of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis.

In allostatic theory, physiological responses in mood disorders and major life events are considered related.[216] Thus, both have been used to model the immunosuppressive effects of psychological stress, showing decreased levels and activity of natural killer cells, increased T-helper/T-suppressor lymphocyte ratio, and lowered lymphocyte proliferative response to mitogen.[215] However, there are also notable differences. Depression has been associated with decreased lymphocyte counts whereas the opposite is observed for stress. Furthermore, immunological differences may be more pronounced in depression than in stress.[215] These findings support that the allostatic load may be greater in pathological states, *e.g.*, depression, than in natural and often more transient stress responses to major life events. Indeed, natural killer cell activity and lymphocyte response to mitogen stimulation are reduced among widows who fulfill criteria for major depression compared with non-depressed widows,[217] and alterations in immune function following negative life events correlate with the severity of depressive symptoms.[218] Studies on whether immune function depends on severity of mood disorders, as measured by need for hospitalization, are scarce.[215]

The possible effect of psychological stress on VZV-CMI in particular is evident by reduced VZV-specific responder cell frequency in patients with major depression compared with healthy controls.[219,220] Furthermore, the Depression Substudy of the Shingles Prevention Study found that immunogenicity of Zostavax was reduced in untreated persons with depression but not among persons treated with antidepressants and non-depressed.[221] Although these findings suggest that psychological stress is linked to decreased VZV-CMI, the clinical relevance in terms of triggering zoster is unclear.

Epidemiological studies on mood disorders and psychological stress as risk factors for zoster are summarized in Table 4. Five cohort studies,[89,90,116,222,223] three case–control studies based on prospectively collected data,[35,100,116] and two case–control studies using self-report data[77,78] have described the association between mood disorder and zoster. The studies included between 42 and 6830 persons who had both mood disorder and zoster diagnosed. Most studies focused on depression. Two Taiwanese cohort studies used the same data source but slightly different methods and definitions.[222,223] In general, cohort and case–control studies based on routinely collected data report that persons with mood disorders have an 11% to 52% increase in the relative risk of zoster compared with persons without depression.[35,100,116,126,222,223] Relative risk estimates from studies using self-reported data, however, vary between 0.93 and 4.15.[77,78,89,90] In addition to

the studies in Table 4, two case–control studies on physical trauma[121] and asthma[86] also included data on depression and 'psychologic conditions' (*e.g.*, mood disorders, behavioral disorders, and adult attention deficit disorder) as covariates, showing conflicting results (ORs 1.13 and 0.79, respectively).

Various limitations hamper the interpretation and comparison of previous studies. First, methods used to define mood disorders vary considerably. For example, some cohort studies used broad definitions where depression was grouped together with bipolar disease, personality disorders, and late psychotic disorder due to alcoholic use,[116,126,223] or where adjustment disorder was classified with anorexia.[223] These conditions may have different etiologies and psychological and physiological consequences, leading to distortion of their potential effects. Second, three studies adjusted for factors that are proxies for the exposures or on the causal pathway (number of claims,[116] use of antidepressants,[222] and self-rated health[89]), which may inevitably have caused overadjustment, as suggested by large difference between unadjusted and adjusted estimates in one study.[222] Third, the studies by Marin *et al.*[78] and Lasserre *et al.*[77] assessed for presence of mood disorder up to 21 days (6 months for controls) after inclusion. The pain from zoster may have affected participants' mental wellbeing, resulting in reverse causation. Fourth, selection bias may have been introduced in these studies due to missing data or if factors affecting participation (*e.g.*, educational status or severity of depression) were related to exposure and a higher or lower risk of zoster.[77,78,89] Similarly, selection bias may have occurred in the cohort study by Schmader *et al.* because of drop-out of patients with severe mood disorder. Finally, the comparison group selected in two cohort studies is of concern.[126,223] Yang *et al.*[223] used a comparison cohort of persons who had no diagnosis of mood disorder during the study period, thus conditioning on information acquired during follow-up. Hata *et al.*[126] compared the risk of zoster in the exposed cohort with persons who had other chronic diseases that may themselves directly or indirectly increase risk of zoster. None of the previous studies have examined whether the risk of zoster depends on time since last diagnosis or severity of mood disorder, which further impedes interpretation. Based on the theory of allostatic load, it seems plausible that an increase in zoster risk would be most pronounced for current and severe mood disorder.

Five studies have used different types of negative life events to study the association between psychological stress and zoster (Table 4). In a self-controlled case series, Harpaz *et al.*[224] found no increase in risk of zoster within 90 days following unexpected health events in a spouse. In contrast, studies examining a wide range of different self-reported negative live events report increased risks of zoster up to 4 years after the interview, with particularly strong associations observed in case–control studies.[77,78,89,225] Additionally, one study reported that widows were not at increased risk of zoster, but data were not shown.[60] Only one study measured level of perceived stress, but the crude comparison of median scores was all that these authors reported.[78] Although these conflicting findings may be attributed to use of different exposure windows and measures of stress, the studies on self-reported negative life events may also have suffered from bias due differential participation or drop-out,[77,78,89,225] misclassification of exposure due to recall,[77,78,89,225] lack of interviewer blinding,[77,78,225] and random error.[77,78,89,225] The overall evidence for an association between psychological stress and zoster thus remains conflicting.

Table 4. Studies on mood disorders and/or negative life events and risk of zoster

Reference	Design, setting, data sources, period*	Population, exposure, outcome, analysis (covariables)†	Results*
Forbes H *et al.*[35]	- CC study - The UK - CPRD and HES - 2000–2011	- Zoster cases (n=144,959) and matched (age, sex, practice) controls (n=549,336) - Record of depression in past year - GP diagnosed zoster and primary hospital zoster diagnoses - Conditional LR (various comorbidities, immunosuppressants, smoking, alcohol)	- Depression, OR=1.15 (99% CI: 1.10–1.19)
Harpaz R *et al.*[224]	- SCCS - US - Truven Health MarketScan Commercial and Medicare Databases - 2002–2011	- Exposed enrollees aged ≥25 y (n=39,811) - Death/ICU-stay of ≥14 days in a spouse (co-beneficiaries of opposite sex and within 5 y of age) aged ≥30 y and with no hospital/institution stay in past year - Registry record of zoster during days 1–90 after vs. 120–31 before exposure. - Conditional Poisson regression and generalized estimating equation methods	- IRR=0.76 (0.54–1.06) - RR=0.99 (0.70–1.39) when considering zoster as proportion of all claims - No variation by age (<60/≥60 y) or when extending period to 30, 60, or 120 d
Hata A *et al.*[126]	- Cohort study - Osaka, Japan - Kitano Hospital Research Database - Sep 2001–Dec 2007	- Adults with hospital contact for 1 of 17 underlying diseases (n=55,492) - Depression registry code (comparison: cohorts without depression) - Zoster registry dx - Cox (age, various comorbidities)	- Depression, HR=1.31 (0.95–1.80)
Joesoef RM *et al.*[116]	- CC study - US - MarketScan data - 2007	- Zoster cases (n=59,173) and frequency-matched (age, insurance plan) controls (n=616,177) aged 20–64 y - Registry dx of depression - Unconditional LR (sex, no. of outpatient claims, various comorbidities)	- Depression, OR=1.52 (1.46–1.58)
Lasserre A *et al.*[77]	- CC study - Mainland France - 121 general practices - Apr 2009–Sep 2010	- Zoster cases aged <50 y presenting within 1 week (n=250) and matched (age, sex) controls with other incident acute diseases (n=500) - Current anxiety or depression (HAD score ≥8) and negative life events (Paykel list) in past 6 mos., assessed at inclusion - GP dx of zoster - Conditional LR (age, sex, education, DM, ulcer, GCs, physical trauma past 2 mos., zoster family history, children in household past 10 y, the other exposures)	- Anxiety, OR=1.07 (0.53–2.15) - Depression, OR=4.15 (1.88–9.16) - Negative life events, OR=3.40 (1.67–6.93)
Liao C-H *et al.*[222]	- Cohort - Taiwan - Longitudinal Health Insurance Database - 2000–2005	- Patients with depression (n=22,886) and frequency matched (sex, age, index year) comparison cohort (n=91,542) - Registry dx of depression - Registry dx of zoster - Cox (age, sex, various comorbidities, antidepressant use during follow-up)	- Depression, HR=1.11 (1.01–1.21); 1.03 (0.92–1.16) for women; HR=1.26 (1.09–1.47) for men - 1.20, 0.95, 1.07, 1.44, 1.00, 1.00 for age <25, 25–34, 35–44, 45–54, 55–64, and ≥65 y, resp.
Liu B *et al.*[90]	- Cohort - NSW, Australia - The 45 and Up study, claims data - 2006–2009	- Persons participating in survey for adults ≥45 y (n=255,024) - Self-reported anxiety/depression ever at baseline - Prescription for or hospital dx of zoster - Cox (age, sex, asthma, immunosuppression, cancer, smoking)	- Depression/anxiety, HR=1.01 (0.95–1.08)
Marin M *et al.*[78]	- CC study - Olmsted County, Minnesota - Rochester Epidemiology Project - Jan 2010–Oct 12, 2011	- Zoster cases aged ≥50 y presenting within ≤72 h (n=389) and matched (birth date, sex) controls seeking care at same clinic closest in time of case (n=511) - Current depression (PHQ-8 score ≥10), new/increased stress and level of stress (from 0 [none] to 10 [worst imaginable]) in past 3 mos.	- Depression, OR=3.81 (2.08–6.98); 2.56 (1.32–4.97) when also adjusted for new increased/stress, sleep disturbance, and weight loss - New/increased stress, OR=2.80 (2.06–3.80); 2.46

		- Validated registry dx of zoster - Conditional LR (age, sex, vaccination status, and immune incompetence)	(1.77–3.41) when also adjusted for sleep disturbance, depression, and weight loss; 1.89 (1.09–3.28) if severe - No difference in median stress score (7 vs. 7)
Ogunjimi B *et al.*[100]	- CC study - Flanders, Belgium - Intego GP registration network - 1994–2011	- Zoster cases aged <60 y (n=3736) and matched (age, sex, practice) controls (n=14,076) - Record of depression in database in past year - Registry dx of zoster - Unspecified LR (none)	- Depression, OR=1.43 (1.07–1.90)
Schmader K *et al.*[89] (reported also in[226])	- Cohort study - North Carolina, US - Duke EPESE - 1989–1994	- Black/white community-dwelling persons aged >65 y (n=4162) - Current depression (≥8 on the modified CES-D scale) and negative life events (GALES scale) in year before survey (performed at 3-y intervals during 1986–1994) - Self-reported physician-diagnosed zoster since last survey - Cox (time-varying age, sex, education, cancer, chronic diseases, basic and instrumental ADLs, self-rated health, hospitalization in past year, and smoking)	- Depression, aHR=0.93 (0.51–1.71) - Negative life events, aHR=1.38 (0.96–1.97)
Schmader K *et al.*[225]	- CC study - North Carolina, US - Observational study - Late 1980s	- Zoster cases aged ≥50 y (n=101) and matched (age, sex, race) controls (n=101) - Negative life events (GALES scale) in past year - Self-reported physician diagnosed zoster - Woolf's method (age, sex, race)	- Negative life events, OR=2.60 (1.13–6.27), 2.64 (1.20-–6.04), and 2.00 (1.04–3.93) within 2, 3, 6 mos. before index date, respectively
Paper II	- Two CC studies - Denmark, 1997–2013 - The UK, 2000–2013 - Various databases	- Zoster cases aged ≥40 y (n=190,671/150,207) and matched (age, sex, practice) controls (n=762,684/576,878) - Partner bereavement - Record of zoster in general practice (antiviral rx as proxy in DK) or hospital - Conditional LR (age, sex, various immunosuppressive diseases and treatments)	- Bereavement ever, pooled OR (99% CI)=1.03 (0.98–1.08), with no variation by time since bereavement - No substantial variation by age, sex, partner's risk of death, or recent depression/anxiety
Paper III	- Two CC studies - Denmark, 1997–2013 - The UK, 2000–2013 - Various databases	- Zoster cases (n=190,671 [≥40 y]/177,361) and matched (age, sex, practice) controls (n=762,684/674,503) - Dx of mood disorder in general practice (UK only) or the hospital-based setting ever - Record of zoster in general practice (antiviral rx as proxy in DK) or hospital - Conditional LR (age, sex, various immunosuppressive diseases and treatments)	- Any mood disorder, OR (99% CI)=1.15 (1.12–1.19) in DK and 1.12 (1.11–1.14) in the UK - OR 1.11, 1.23, and 1.24, for depression, anxiety, and severe stress and adjustment disorder in DK - OR 1.12, 1.12, and 1.14, for depression, anxiety, and severe stress and adjustment disorder in the UK
Yang *et al.*[223]	- Cohort study - Taiwan - Longitudinal Health Insurance Database - 2004	- Psychiatric patients ≥18 y (n=42,340) and matched (age, sex) comparison cohort (n=169,360) - Various mood disorders, *e.g.*, affective psychoses (depression, bipolar disease; n=4728), neurotic illness (phobia, anxiety, OCD, personality disorders; n=19,643), and other (adjustment disorder, anorexia; n=12,766) - Zoster registry dx during follow-up (until end of 2006) - Cox (age, sex, SES, comorbid disorders and immunosuppressive drugs)	- Any psychiatric disease, HR=1.29 (1.18–1.38) - Age ≤60 y: HR=1.34 for affective psychoses, 1.42 for neurotic illness, and 1.53 for other mental disorders - Age >60 y: HR 0.93 for affective psychoses, 1.26 for neurotic illness or personality disorders, 1.15 for other mental disorders

Abbreviations: ADL=activities of daily living; CC=case–control; CI=confidence interval; CES-D=Center For Epidemiological Studies-Depression scale; Cox=Cox proportional hazards regression; CPRD=Clinical Practice Research Datalink; DK=Denmark; dx=diagnosis; EPESE=Established Populations for Epidemiological Studies of the Elderly; GALES=the Geriatric Scale of Recent Life Events; GC=oral glucocorticoid; GP=general practitioner; HAD=Hospital Anxiety and Depression Scale; HES=Hospital Episodes Statistics database; HR=hazard ratio; ICU=intensive care unit; LR=logistic regression; mo=month; NSW=New South Wales; OCD=obsessive compulsive disorder; OR=odds ratio; PHQ-8=Patient Health Questionnaire-8; RR=risk ratio; rx=prescription; SCCS=self-controlled case series; SES=socioeconomic status; UK=United Kingdom; US=United States of America.
*Fully adjusted estimates are presented. Parentheses: precision measured using 95% CIs unless otherwise stated.

2.7.4 Occult cancer

The increased risk of zoster among cancer patients has primarily been ascribed to immunosuppression from radiation and chemotherapy.[155] However, carcinogenesis can in itself induce immune deficiency.[227] This phenomenon is particularly pronounced in hematological cancers, where counts and activity of B- and T-cells are decreased.[227] It has therefore been suggested that occult (undiagnosed) cancer may also trigger zoster and that zoster may even serve as a clinical marker of cancer (*i.e.*, a paraneoplastic syndrome) that can facilitate diagnosis at an earlier stage.[228-230] However, in the absence of systematic reviews on the topic, such arguments have been made based on single studies.

Our systematic review revealed 46 eligible studies on the association between zoster and subsequent cancer. Most focused on hematological cancers. A complete overview of the studies, including references, is provided in paper IV (Tables 1, 3, and 4).[231] Although several studies were aimed at investigating zoster as a risk factor for cancer and therefore discarded diagnoses in the first years after zoster, we included all studies for completeness. Ten studies reported estimates for all cancers combined.[228,229,232-239] We used a random effects meta-analysis to pool the results for cancer overall, for any hematological cancer, and for individual types of cancer. For overall cancer, we performed analyses for the first year of follow-up after zoster, as our primary aim was to investigate zoster as a marker of occult cancer. The meta-analysis should be interpreted with caution because of statistical heterogeneity. We pooled the results despite this variability because the direction of effect estimates was uniform and because it allowed us to investigate reasons for differences.

The forest plot in Figure 4 shows the results from studies reporting on all cancers combined. The pooled relative risk of cancer after zoster was 1.42 (95% confidence interval [CI]: 1.18–1.71), increasing to 1.83 (95% CI: 1.17–2.87) when considering estimates for the first year of follow-up. However, healthcare contact due to zoster may have increased the chance of detection of cancer, leading to an upwards bias of estimates especially in the first year. Furthermore, there was large variation in estimates, and several studies had methodological shortcomings. After excluding studies considered at high risk of bias, the pooled relative risk remained increased. Nevertheless, statistical heterogeneity remained high. In studies reporting absolute risk measures, risk of cancer within the year after zoster also varied considerably (0%–1.1%). A higher one-year risk (1.8%) was detected in a study of inpatients with zoster. One study found cancer in 4.6% of zoster inpatients examined with chest X-ray, gastric endoscopy, and abdominal computed tomography scan.

As expected, analyses of individual cancers showed strong associations between zoster and hematological cancers (Figure 5). Considering studies on any hematological cancer, the pooled relative risk was 1.60 (95% CI: 1.46–1.75) overall, 1.66 (95% CI: 1.47–1.87) after restricting to studies at low risk of bias, and 2.40 (95% CI: 1.62–3.55) when further restricting to studies that did not discard cancers diagnosed in the first year after zoster. Pooled relative risks were generally higher for lymphoid hematological cancers than for myeloid subtypes. We found lower estimates for solid cancers (between 0.63 and 2.18) than for hematological cancers, especially when considering timing since zoster diagnosis (Web Table 5 in Paper IV). For any cancer and individual cancers, the relative risk decreased with time passed since zoster (Web Tables 3 and 5 in Paper IV). The elevated risk of hematological cancers persisted even 5–10 years after zoster.

Figure 4. Relative risk (95% confidence interval) for the association between zoster and subsequent cancer

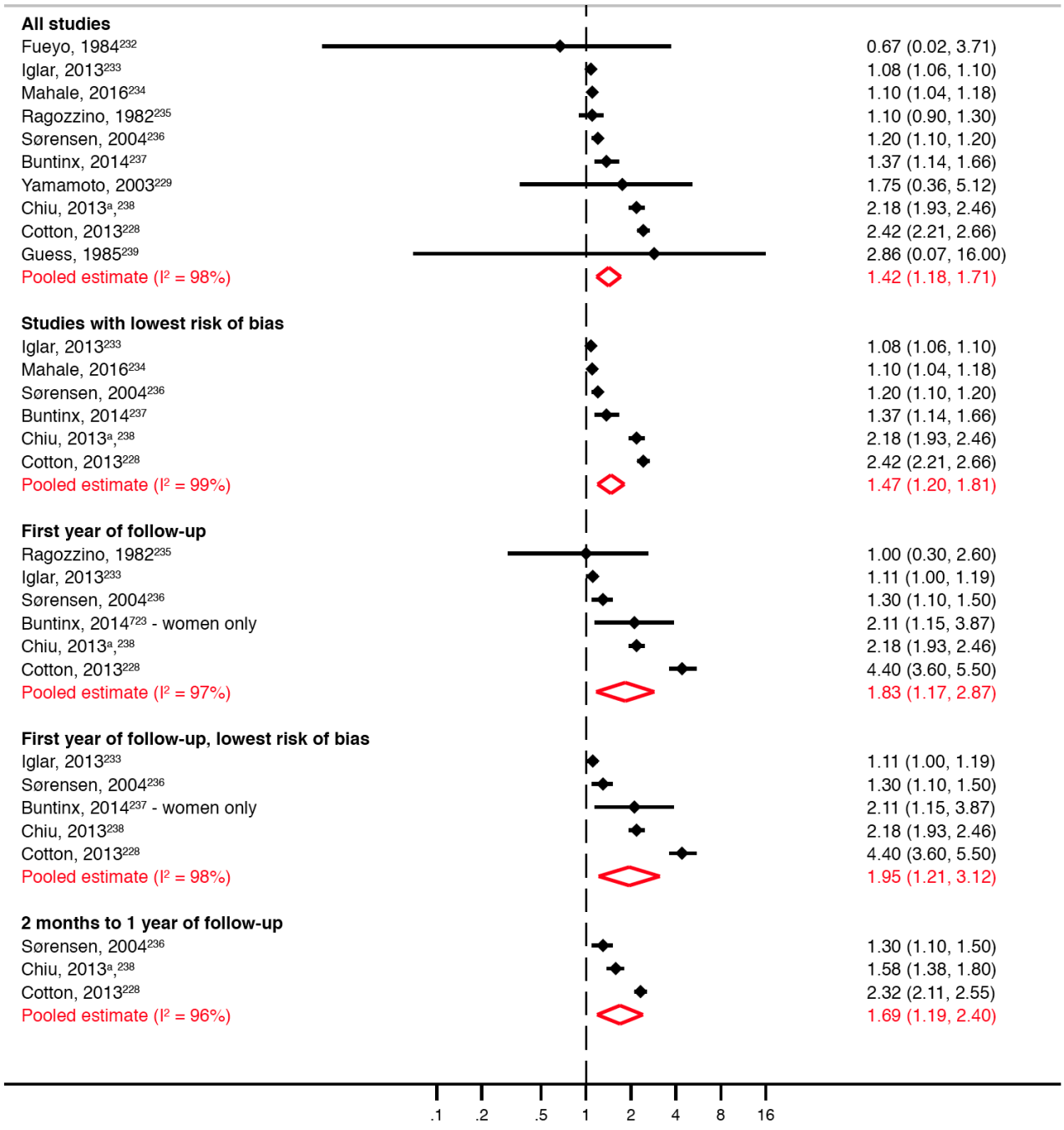
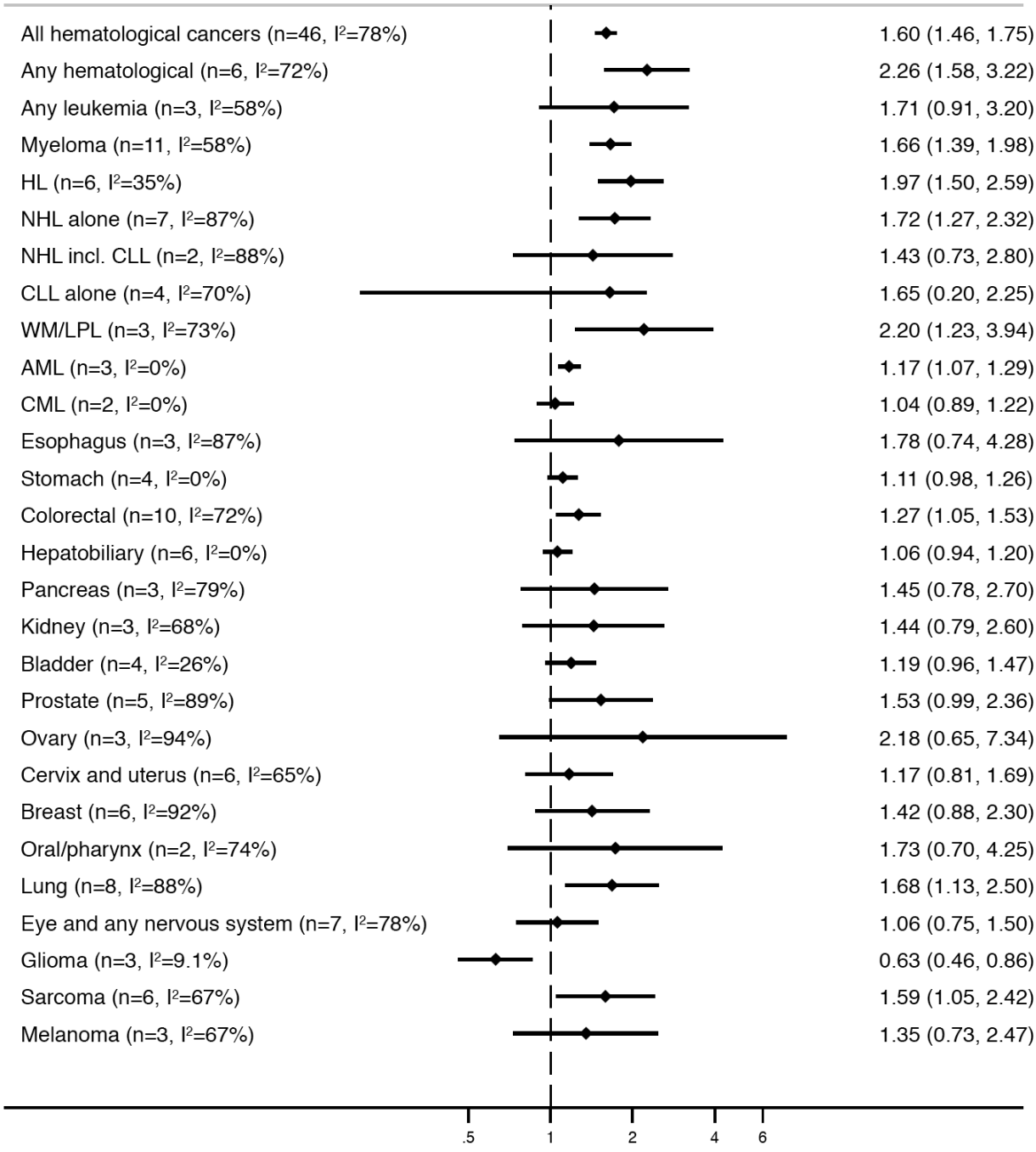


Figure 5. Relative risk (95% confidence interval) for the association between zoster and subsequent cancer. The number of studies and I^2 statistic is shown in parenthesis. References are provided in study IV in the Appendix



2.8 Summary of literature review

Data on the occurrence of zoster in the general population, as well as the hospital-based setting where treatment costs typically are high, are pivotal for evidence-based decision-making about implementing routine vaccination. Our review of the literature shows that data on rates of zoster in Europe, including Denmark, are sparse. In accordance, the WHO[26] and the European Centre for Disease Prevention and Control[22] have stressed a need for a better understanding of the epidemiology of zoster. Zostavax is costly,[25] so quantification of risk factors for zoster may help optimize vaccination strategies through prioritized vaccination of high-risk groups. However, relative risk estimates for both established and possible zoster risk factors vary substantially, and few well-controlled large population-based studies have been published.

In addition to informing vaccine policy, studies on risk factors for zoster may increase our understanding of this common disease. They may provide insights into reasons for the increasing rates of zoster and help identify relevant health interventions in the population. Although severe immunosuppression is a well-established risk factor for zoster, over 90% of persons diagnosed with zoster are not identified as immune incompetent.[36,240] Considering that one third of the population is estimated to develop zoster, surprisingly little is known about other risk factors. Evidence on lifestyle factors and related diseases, such as COPD and diabetes, is conflicting. Furthermore, although psychological stress is commonly cited as a risk factor for zoster, observational studies are sparse, and most are potentially biased. This lack of sound epidemiological evidence is likely explained by difficulties in measuring psychological stress because perception of an event or situation as stressful or not is subjective and depends on coping mechanisms.[216]

The hypothesis that zoster may be triggered by occult cancer has also been debated for decades. Our systematic review for paper IV shows evidence that zoster may be a marker for occult cancer, providing support for this hypothesis. However, the absolute risk of cancer in zoster patients seems to be low. In addition, there are no studies on benefits and harms of using diagnostic procedures to detect cancer in patients presenting with zoster. The current evidence base thus does not support extensive examination for cancer beyond that indicated by the regular anamnesis and physical examination.

2.9. Aims of the thesis

The overall aim of this thesis was to address some of the current gaps in our understanding of the epidemiology of zoster. In **paper I**, we developed an algorithm for identifying zoster based on routinely collected data on dispensed prescriptions and hospital records. We applied the algorithm in Denmark to (i) validate antiviral prescriptions as proxies for zoster, (ii) estimate the occurrence of zoster, and (iii) quantify relative risks of zoster associated with various chronic conditions and medications, including more controversial factors, such as COPD, asthma, diabetes, CKD, and inhaled GCs. In **paper II**, we examined if depression, anxiety, and severe stress and adjustment disorder were associated with zoster, hypothesizing that chronic psychological stress in these mood disorders reduces VZV-CMI. In **paper III**, we explored the role of psychological stress further by using partner bereavement as a proxy because this major life event is considered to be extremely stressful for most persons, regardless of coping mechanisms.

3. Methods

This chapter describes the material and methods used for studies I–III. An overview is provided in Table 5.

3.1 Setting

Study I was conducted in Denmark, whereas studies II and III additionally included data from the United Kingdom (UK). Both Denmark and the UK have rich sources of data with complementary strengths and weaknesses.[241,242] We envisioned that use of data from both settings would provide a sounder evidence base by allowing us to include more study subjects, to explore potential effect modifiers in various ways, and to perform more detailed analyses of potential sources of systematic error (*e.g.*, residual confounding). We hoped that replicability in two different settings would thus provide credence to our findings.

Denmark and the UK have tax-financed healthcare systems, guaranteeing prepaid access to care for all residents.[243,244] General practitioners are the cornerstone of the primary healthcare sector and serve as gatekeepers to secondary care services, including treatment at hospitals and by private practicing specialists (*e.g.*, ophthalmologists and psychiatrists). General practice is similarly structured in Denmark and the UK, but differ slightly with regard to, *e.g.*, remuneration (larger part based on capitation in the UK and on fee-for-service in Denmark) and structure of out-of-hours services.[245,246] Partial copayment of prescription drugs is required for Danish and some English residents whereas Wales, Scotland, and Northern Ireland have fully abolished prescription charges.

Varicella vaccination is not part of the routine childhood vaccination schedules in Denmark and the UK but is recommended for susceptible adults and for seronegative immunosuppressed persons (*e.g.*, before organ transplantation or leukemia treatment), as well as susceptible household contacts to these persons.[247,248] In Denmark, there are no official guidelines for use of Zostavax, which was marketed in September 2014. According to statistics for gross sales of drugs, only 900 and 1300 units of Zostavax were sold in Denmark in 2014 and 2015, respectively.[249] In the UK, Zostavax vaccination has been offered since September 2013 to all people aged 70 years with a catch-up program for those aged 71–79 years.[27] Vaccine uptake was approximately 50%–60% as of August 2016.[27]

3.2 Study designs and populations

Study I included a cross-sectional random sample of patients from nine Danish practices as part of a validation study, as well as a cohort design to study rates of zoster in the entire Denmark. To study risk factors of zoster in studies I–III, we used an incidence-sampling case–control design.[250,251] The case–control design was selected because it allowed us to examine a wide range of potential risk factors after sampling the study population only once. The study populations included cases of zoster and matched controls.

Table 5. Summary of material and methods

	Study I	Study II	Study III
Objectives	To validate an algorithm to identify zoster based on rx and hospital data and use it to quantify zoster rates and risk factors in Denmark.	To examine the association between extreme stress, as measured by partner bereavement, and risk of zoster.	To examine the association between mood disorders and risk of zoster.
Setting	DK (1997–2013).	DK (1997–2013) and the UK (2000–2013).	DK (1997–2013) and the UK (2000–2013).
Design	Cross-sectional (validation), cohort, incidence density case–control study.	Incidence density case–control study.	Incidence density case–control study.
Data sources	The health information system for the Central Denmark Region, National Prescription Registry, DNPR, CRS.	The Danish National Prescription Registry, DNPR, DPCR, the National Diabetes Registry, CRS, the Population Education Registry; The UK CPRD, HES, IMD.	The Danish National Prescription Registry, DNPR, DPCR, the National Diabetes Registry, CRS, the Population Education Registry; The UK CPRD, HES, IMD.
Study population	Validation sample for rx-based definition (n=176); all persons with incident zoster in DK (n=189,025); controls matched by age and sex (n=945,111).	Persons with zoster in DK (n=190,671) and in the UK (n=150,207) at age ≥40 y; controls matched to cases by age and sex in DK (n=762,684) and also by practice in the UK (n=576,878).	Persons with zoster in DK (n=190,671; ≥40 y) and in the UK (n=177,361; ≥18 y); controls matched to cases by age and sex in DK (n=762,684) and also by practice in the UK (n=674,503).
Exposures	Age, sex, calendar time, RA, SLE, IBD, COPD, asthma, diabetes (type I, type II, or unknown), CKD, HIV, HSCT, other cellular immune deficiency, leukemia, lymphoma, myeloma, depression, inhaled GCs, oral GCs, other immunosuppressants.	Partner bereavement.	Mood disorders (depression, anxiety, severe stress and adjustment disorder).
Subgroups	Age, sex, and calendar year of prescription for validation study; setting (rx-based or hospital-based) for study of occurrence and risk factors.	Time since bereavement; exposure within 30 days before index date: partner's risk of death (predicted by the ACCI, and in the UK, terminal disease), age, sex, current depression/anxiety.	Timing of mood disorder grouped as current, recent, or former, and severity grouped as mild, moderate or severe.
Outcome	Zoster; accuracy of prescription as a proxy	Zoster.	Zoster.
Covariables	Each exposure was mutually adjusted for the other factors of interest.	All exposures from study I; SOT; SES (education level/IMD), lifestyle factors in the UK (smoking, alcohol, BMI).	All exposures from study I; SOT; SES (education level/IMD), lifestyle factors in the UK (smoking, alcohol, BMI).
Statistical analysis	Calculation of PPVs, age-specific rates, direct standardization, and conditional logistic regression.	Conditional logistic regression.	Conditional logistic regression.

Abbreviations: BMI=body mass index; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; DK=Denmark; GC=glucocorticoid; HIV=human immunodeficiency virus; HSCT=hematopoietic stem cell transplantation; IBD=inflammatory bowel disease; IMD=Index of Multiple Deprivation; PPV=positive predictive value; RA=rheumatoid arthritis; rx=prescription; SES=socioeconomic status; SLE=subacute/systemic lupus erythematosus; SOT=solid organ transplantation; UK=United Kingdom.
All variables are listed in the overview table and defined in detail in the research papers (appendix). The Jan 2014 build of CPRD was used including both clinical and referral files to identify diagnoses.

3.3 Data sources

The studies were based on various Danish and British databases. All data sources were population-based, *i.e.*, they provided complete coverage of disease occurrence in well-defined geographic populations.[44]

3.3.1 Denmark

In Denmark, we used seven databases covering various aspects of medical care and education. Data are routinely collected using the central personal registration (CPR) number, which is assigned to residents at birth or at immigration.[252] The CPR number is unique and permanent, thus allowing individual-level linkage of data sources in a simple and unambiguous manner.

The Danish National Prescription Registry includes anonymized data on prescriptions filled at Danish community pharmacies since January 1, 1995.[253] When a person fills a prescription at the pharmacy, the patient's CPR number, dispensing details for the drug, and identifiers for the issuing physician and the pharmacy are logged by the electronic accounting system and transferred to the registry.[253] Variables for indication and dosing instructions are available since April 2004, but are recorded inconsistently. Regional sources with data on reimbursed prescriptions are also available in Denmark and provide the possibility of obtaining non-anonymized prescription records for studies where access to medical journals is required. For the validation in paper I, we obtained such data, which was collected by the Aarhus University Prescription Database and recorded in *the health information system for the Central Denmark Region*.[254]

There are two Danish discharge registries, *the Danish National Patient Registry*[241] and *the Danish Psychiatric Central Registry*,[255] which were merged in 1995. These registries collectively provide data on all psychiatric admissions since 1970, somatic admissions since 1978, and contacts to psychiatric and somatic hospital outpatient clinics and emergency rooms since 1995.[241,255] At the end of each contact, a primary diagnosis (the main reason for contact) and optional secondary (contributing) diagnoses are recorded by the physician in charge.[241] Diagnoses were coded using the International Classification of Diseases (ICD), 8th revision until 1994, when it was replaced by the ICD-10. Surgical and non-surgical procedures and treatments are also registered.

The Civil Registration System is key to Danish registry-based research because it is responsible for assigning the CPR number and provides a complete account of the entire Danish population on a day-to-day basis.[252] The registry was established in 1968 and records dates of birth, death and emigration, address, civil status, and kinship (CPR number of parents, spouse, and children) for all residents.

The Danish National Diabetes Registry identifies patients receiving care for diabetes in primary and/or secondary care since 1995.[256] A person becomes eligible for the registry when diagnosed with diabetes in the Danish National Patient Registry; after a record of chiropody, ≥5 blood glucose measurements during a 1-year period, or ≥2 yearly blood glucose measurements during 5 consecutive years in the National Health Service Registry; or when dispensing a second prescription for insulin or any oral anti-diabetic drug according to the Danish National Prescription Registry. The completeness and positive predictive value (PPV) of diagnosed diabetes are both estimated at approximately 90%.[256]

The Population Education Registry registers the highest attained education for residents based on administrative records from educational institutions, supplemented with self-reported data for individuals completing education before 1974 and immigrants with schooling outside Denmark.[257] In 2007, 3% of ethnic Danes born in 1945–1990 had missing data, increasing to up to 15% for immigrants.

3.3.2 The UK

In the UK, the main data source was *the Clinical Practice Research Datalink* (CPRD). The CPRD includes data from over 12 million patients from more than 680 general practices.[242] Approximately 5 million persons (7%) of the current UK population are registered in the CPRD. Although a practice participates in the CPRD, individual patients can request to opt out. Vast healthcare data are recorded in the datalink, including symptoms and diagnoses leading to consultation, written prescriptions, laboratory and clinical measurements (*e.g.*, anthropometric measures), vaccinations, referrals to secondary care services, and health-related behaviours.[242] Data are collected by general practice staff through the electronic patient record systems and transferred to the CPRD secure servers. At the research service, quality checks are performed on practice-level (*e.g.*, requiring a set minimum referral rate) and patient-level (*e.g.*, requiring non-missing data on birth year) to identify data considered up-to-standard and acceptable for use in research. Basic demographics (age, sex, and ethnicity) of the CPRD population are similar to the UK population. Linkage of CPRD data to other data sources is possible for practices consenting to the so-called linkage scheme (approximately 60%).

Since 1989, *the Hospital Episode Statistics* (HES) *database* collects data on diagnoses and procedures for inpatient contacts to English hospitals funded by the National Health Service (NHS) trust.[258] Data for the CPRD linkage scheme are available since April 1997, and linkage is based on eight sequential steps using deterministic matching on NHS number, sex, and partial/full birth date. A hospitalization in HES relates to an entire hospital stay from admission to discharge, taking transfers in a fiscal year into account.[258] A hospital stay may consist of one or more episodes, defined as the time period where the patient is under continuous care of one consultant (*i.e.*, using the beds of one healthcare provider). For each episode, a primary diagnosis (typically the main reason for admission), up to 19 secondary diagnoses, and 24 procedures are recorded. Coding from physicians' medical notes is outsourced to clinical coders. Data from outpatient clinics have been available only since September 2014 and are not included in this thesis.

The Index of Multiple Deprivation (IMD) is a system used to estimate the level of deprivation in a small geographical area with about 1500 residents.[259] The IMD score is computed by weighing 38 indicators within seven domains covering various socioeconomic aspects (income, employment, health and disability, education, skills and training, barriers to housing and other services, crime, and living environment). The score is categorized in quintiles of increasing level of deprivation. The area scores are mapped to the postcode of a person's general practice or home to yield a measure of relative deprivation on practice- and patient-level. The IMD 2010 dataset contains practice-level scores for all CPRD practices while patient-level scores are available for persons with valid postcodes and registration with a practice of the CPRD linkage scheme.

3.4 Definition of herpes zoster (outcome)

3.4.1 Denmark

The long tradition for keeping records of residents' healthcare utilization in Denmark provides a unique opportunity to study the epidemiology of many diseases.[252] However, data from general practice and private practicing specialists are often lacking, including diagnoses of zoster. We therefore developed an algorithm where zoster was defined as either (i) a hospital-based inpatient, outpatient, or emergency room diagnosis of zoster in the Danish National Patient Registry or (ii) a prescription for systemic acyclovir, valacyclovir, or famciclovir in the Danish National Prescription Registry. The main competing indications for the antivirals are severe primary and reactivating herpes simplex infections, which are most frequent at young age[260] and may require repeated (continuous or periodic) antiviral therapy.[261] To increase the specificity of our algorithm for zoster, we therefore included only persons who were aged 40 years or older and who had not previously filled a prescription for one of the antivirals. To ensure at least 2 years of prescription history to exclude previous treatment, the study period was January 1, 1997, to December 31, 2013. We tested two prescription-based definitions for identifying zoster: (i) a 'broad definition', including first-time antiviral prescriptions at any dose and (ii) a 'zoster-specific definition', where we required that the first-time prescription was for a tablet dose commonly used for zoster. For acyclovir, this included 800 mg tablets in packages containing 35 pills, consistent with a 7-day supply. For valacyclovir and famciclovir, prescriptions for 500 mg tablets in any package size were considered because data in the Prescription Registry made it more difficult to differentiate between treatments for different herpes infections. All three antivirals are covered by the general reimbursement scheme in Denmark[262] and are thus recorded in both national and regional sources of prescription data.[253,254]

The date of hospital diagnosis or defining prescription was taken as the diagnosis date for zoster ("index date"). If a person had both a relevant diagnosis and prescription, we used the earliest record giving priority to hospital diagnoses. When we performed separate analyses for the hospital-based setting (study I), we ignored whether a person had filled an antiviral prescription prior to contact, in order to provide a complete picture of the need for hospital referral.

We validated the prescription-based definitions using data from the health information system for the Central Denmark Region (study I). Due to constrains in resources, we selected 10 practices among a group of research active general practitioners that were active in the Central Denmark Region at the time of study (September 2016). We restricted to general practitioners because they account for the majority of antiviral prescriptions. For practices that agreed to participate, we randomly sampled up to 20 patients identified by the broad definition between January 1, 2007, and December 31, 2012, and who had resided in the study region for at least 2 years at the time of prescription. We asked practices to identify the indication for treatment (zoster, herpes simplex, other, or unknown) for each patient in the electronic patient record system.

3.4.2 The UK

In the case–control studies set in the UK, zoster cases were identified based on diagnoses in the CPRD or HES between January 1, 2000, and December 31, 2013 (studies II and III). To avoid including records representing history of zoster documented shortly after registration with a new practice, we excluded cases who had been listed with their current practice for less than one year. We restricted to data that were deemed up-to-standard and acceptable for research. We defined the index date as the date of consultation or hospital admission for zoster, whichever occurred first for cases with multiple records.

3.4.3 Differences between outcome definitions

Consistent with the aims, the outcome definitions in the studies varied slightly with regard to diagnoses included and choice of index date. In studies II and III, we were particularly interested in whether the relative risk of zoster depended on time since partner bereavement or last diagnosis of mood disorder. Furthermore, we were concerned about reverse causality when studying mood disorders, as neuralgia in zoster can impact mental health/state.[4] In these studies, we prioritized accurate records of the onset of zoster, *i.e.*, that the date of diagnosis was as close as possible to the date of rash onset. Unfortunately, in the hospital registries, only start and end dates of a hospital contact are recorded. Thus, we knew only that the zoster diagnoses were made sometime during this interval, which can be long in some instances (*e.g.*, for psychiatric admissions or outpatient contacts). However, we assumed that if zoster was coded as a primary diagnosis (the main reason for contact), it would have been present at first hospital contact. Based on this assumption, we included only primary hospital-based diagnoses of zoster and defined the date of hospital diagnosis as the start date for a hospital contact (date of admission or start of outpatient follow-up in Denmark and episode start date in the UK). We excluded persons where first diagnosis of zoster was a secondary hospital-based diagnosis and persons with previous diagnoses that could possibly represent a long-term complication of zoster, namely codes for PHN or other nervous system involvement (except meningo-encephalitis).

In study I, one main objective was to describe the occurrence of zoster in Denmark. We therefore prioritized a more complete definition including all primary and secondary hospital diagnoses of zoster. We took the discharge date to be the index date, to be certain that diagnosis of zoster had occurred at that time. This increased sensitivity may have come at the expense of a more accurate diagnosis date and inclusion of only acute zoster; however, we considered this of less importance for estimation of rates, as patients with late complications of zoster would recently have had zoster. Furthermore, because zoster has not been implicated in the pathogenesis for exposures considered in study I, reverse causality was not a concern.

3.5 Matched controls

In our analyses of zoster risk factor, we used population controls to estimate the exposure prevalence in the source population giving rise to zoster cases.[250] Population controls are considered to be associated with less selection bias than, *e.g.*, hospital controls because they are selected without reference to factors that may be associated with exposures of interest.[250]

We used incidence-density sampling to identify up to five controls individually matched to each person with zoster (cases) by birth year/age, sex, and general practice (UK only). Use of more than five controls does not increase precision.[263] In this sampling strategy (also called risk-set or concurrent sampling), all persons who fulfill the matching criteria and who are alive on the index date for the case are eligible as controls.[250] Cases are also eligible as controls before their index date, and a person can be sampled as a control multiple times. Controls are allotted the same index date as cases. Because the chance of repeated sampling is proportional to person-time at risk in the database, odds ratios (ORs) originating from this design approximate rate ratios rather than ORs in the traditional sense.[250] Nevertheless, we have maintained the term ORs in the thesis to avoid confusion. Incidence-density sampling is favored over, *e.g.*, cumulative sampling of controls by the end of the study period because the method is less prone to time-window bias.[264]

We used matching to improve the efficiency of our multivariable stratified analyses, where the inclusion of a large number of explanatory variables came at the risk of empty strata.[265] Matching also increased the efficiency of adjustment for practice (a nominal variable with many categories) in the UK.

We applied the same exclusion criteria for cases and matched controls. To avoid overestimation of effect measures resulting from inclusion of inactive persons from the CPRD, we also excluded matched controls without any consultation record within 6 months before to 12 months after the index date.

3.6 Risk factors of interest (exposures)

3.6.1 Non-psychiatric diseases and treatments (study I)

In study I, our risk factors of interest were age; sex; calendar period of diagnosis; RA, SLE, IBD, COPD, asthma, diabetes (type I, type II, or unknown type), CKD, HIV infection, hematopoietic stem cell transplantation (HSCT), or other cellular immune deficiency at any time before the index date; leukemia, lymphoma or myeloma within 2 years before the index date; depression within one year before the index date; and prescription records for oral GCs, other immunosuppressant drugs (*e.g.*, chemotherapy), or inhaled GCs within 90 days before the index date. Variable definitions are described in detail in the research papers. We also created a combined variable for severe immunosuppressive factors that may contraindicate vaccination (HIV, leukemia, lymphoma, myeloma, HSCT, other cellular immune deficiency, and use of oral GCs or other immunosuppressants). When relevant, we combined data on prescriptions and hospital diagnoses, treatments, and procedures to increase sensitivity of variables. We used definitions that resembled those from the largest study on zoster risk factors in the general population published to date (a case–control study based on the UK CPRD)[35] to enable validation of our zoster algorithm against an external reference standard.

3.6.2 Partner bereavement (study II)

In study III, our exposure of interest was partner bereavement, as a measure of extreme psychological stress. In Denmark, we used an algorithm based on data recorded in the Civil Registration System.[266] In this algorithm, two persons are considered partners if they are married, are in a registered partnership, or live at

the exact same address and have at least one cohabitating child together. Persons who live at the same address but have no cohabitating common children (except stepchildren) are also considered partners if no other adults live at the address and if the two persons are of opposite sex, have an age difference of less than 15 years, and are not closely related according to kinship data in the registry. We classified cases and controls who experienced partner death before index date as exposed from the date of death.

In the UK data, we had no information on patient identifiers for family members or exact address. However, people in a practice who share household or who are otherwise associated can be identified by a 'family number' in CPRD. We therefore adapted an algorithm that identified different-sex couples with an age difference of 10 years or less as partners if they shared a family number.[267-269] We also required that there was no other person in the household within 15 years of either of the couple. As we were concerned about misclassification introduced by use of the family number for entire institutions (*e.g.*, nursing homes) or blocks of flats, we did not consider persons to be partners if the case or control had a code indicating residence in a communal establishment before index date, if both were aged 95 years or older, or if the family number was used for more than 10 persons. Furthermore, we limited to strata where the zoster case was aged 40 years or older, to avoid misclassifying friends sharing residence (assumed less common at older ages). We took the death date in the deceased partner's primary care record as the date of bereavement.

In both Denmark and the UK, we grouped exposed persons according to whether partner bereavement had occurred within 0–7 days, 8–14 days, 15–30 days, 31–90 days, 91–365 days, 366–1095 days, or >1095 days of the index date. As data on time-dependent fluctuations in immune function after stress are limited, we selected cutoffs pragmatically based on an assumption that the greatest reduction in immunity would occur sometime within the first 90 days. We also hypothesized that unexpected bereavement would result in more extreme stress and immunosuppression. We therefore grouped exposure according to partners' risk of death, as predicted by the age-adjusted Charlson Comorbidity Index.[270,271] This classification includes 19 groups of chronic diseases, which are scored at 0–6 points based on the ability to predict death. In the age-adjusted version, additional points are given according to age in 10-year age groups. We computed the total score for deceased partners based on cumulative medical history in the registries, excluding records in the last month before death to avoid causes of death coded retrospectively. We categorized risk of death as low (0–3 points), intermediate (4–6 points), or high (≥7 points). In the UK, we also classified partners according to presence of codes for terminal disease (*e.g.*, delivery of end of life care) at the time of death.

3.6.3 Mood disorders (study III)

In study III, we identified any diagnosis of depression, anxiety, and severe stress and adjustment disorder among cases and controls before index date in the Danish hospital registries and in the UK CPRD and HES. The main exposure was any history of these mood disorders, but we were also interested in whether any association with zoster depended on time since last diagnosis. Based on the most recent record, we therefore differentiated between current (≤90 days before the index date), recent (>90–365 days before the index date), or former (>365 days before the index date) diagnosis. We included codes for remission in the former group.

To contribute to the understanding of potential effect modification by severity, we grouped patients by codes for referral to mental health services and hospital-based treatment within 90 days before the index date. We classified patients who had been hospitalized due to their mood disorder in the 'severe' group. 'Moderate' mood disorder included those who had any other hospital diagnosis for the condition in Denmark and those who had been referred from general practice to a mental health service (*e.g.*, a psychiatrist) in the UK. We classified remaining patients in the 'mild' group, although we recognized that exposure would be relatively more severe for this category in Denmark, where we lacked diagnoses from general practice.

3.7 Statistical analysis

In the validation study, we computed the PPV with 95% CIs[272] of antiviral prescriptions as a proxy for zoster, as the proportion of persons who had zoster as a treatment indication according to the patient record.

We estimated the occurrence of zoster in Denmark using an algorithm combining hospital-based diagnoses and the most accurate prescription definition from the validation study. We obtained population denominators on January 1 each year from the Danish census, which is derived from the Civil Registration System and available online.[273] We plotted age-specific rates in a graph with rates from other European countries to get a crude estimate of completeness of our algorithm. We performed analyses based on the overall algorithm, as well as separately for diagnoses in the hospital-based setting. We also estimated the changes in rates (directly age-standardized to 2000 Danish census data), median age at diagnosis, and prevalence of risk factors among zoster patients during the study period.

In all three studies, we created contingency tables for demographic characteristics, exposures of interest, and other zoster risk factors. In the case–control studies, we used logistics regression to compute ORs with 99% CIs for each risk factor among cases *vs.* controls. We accounted for the potential selection bias introduced by matching on factors associated with exposure by conditioning all analyses on the matching factors.[265] For each risk factor, we compared the unadjusted model with models additionally adjusted for the other zoster risk factors. In study I, we specifically compared multivariable models with and without adjustment for use of inhaled GCs, oral GCs, and other immunosuppressive treatments, to explore if associations were mediated through treatment. We also examined ORs for patients identified by antiviral prescriptions and hospital-based diagnoses separately, to identify factors that may predict hospital treatment. In the bereavement study, we included various risk factors as potential confounders on the suspicion that partners share certain health-related behaviors, which in turn may be associated with mortality and an increased risk of zoster. Similarly, as multimorbidity may affect mental health,[274] we included various chronic conditions as covariables in the mood disorder study.

In the bereavement study, we pooled the Danish and UK estimates using DerSimonian and Laird's random-effects model.[275] We estimated statistical heterogeneity with the I^2 statistic, which measures the percentage of inconsistency that is not attributed to chance alone. We did not combine estimates for mood disorder because we considered exposure data to be too heterogeneous from a methodological perspective.

We investigated effect measure modification by age and sex through stratified analyses. In the bereavement study, we stratified ORs for bereavement within 0–30 days before index date. We also stratified by records indicating diagnosis of depression or anxiety in 90 days before index date because these conditions could be on a causal pathway linking bereavement to zoster.[217,218] In study III, we stratified results for current mood disorder by age and sex. We also examined whether the association was more pronounced for new-onset conditions, defined as first-time record in the current exposure window. Finally, to estimate the potential public health impact of our findings, we assessed for effect modification by age on the absolute scale by multiplying the age-specific ORs for any previous mood disorder in the Danish and UK data by the corresponding absolute rates of zoster in the entire CPRD population in 2010.

We performed various sensitivity analyses to assess robustness to assumptions and decisions in the design and analytical phases. In studies II and III, we repeated the analyses in the Danish data after excluding case–control strata where the case was identified by a prescription without a zoster indication code (not considered sufficiently complete and specific for use in the main analysis). Furthermore, we examined the impact of adjusting for socioeconomic status, as measured by length of education (≤10 years, >10–15 years, or >15 years) in Denmark and quintiles of person-level IMD in the UK. In the UK, we also included data on smoking status (current smoker, ex-smoker, non-smoker), alcohol consumption (current drinker, ex-drinker, non-drinker), and BMI (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2). Almost 90% had complete data on all three variables. In study II, we also performed sensitivity analyses where we repeated stratified analyses with a 90-day exposure window (in case of a later-than-expected effect on immune function) and where we restricted the main comparisons to non-single subjects. In paper III, we performed sensitivity analyses for our exposure definitions, where we (i) included data on antidepressant prescriptions as a proxy for mood disorder in Denmark and as a measure of moderate mood disorder in the severity analysis (although less severe than need for referral or hospital-based treatment), (ii) varied the cut-off between 'current' and 'recent' mood disorder to 7, 14, 30, and 180 days, (iii) excluded those with only possible or unspecific diagnosis codes from the exposed group, and (iv) excluded those with more than one subtype of mood disorder to examine associations for each disease independently. To ensure that poor vaccine uptake in patients with mood disorder could not explain a potentially increased risk of zoster, we examined the impact of ending the study period at the time of marketing of Zostavax (August 31, 2014, in the UK; not applicable in Denmark).

3.8 Ethical considerations

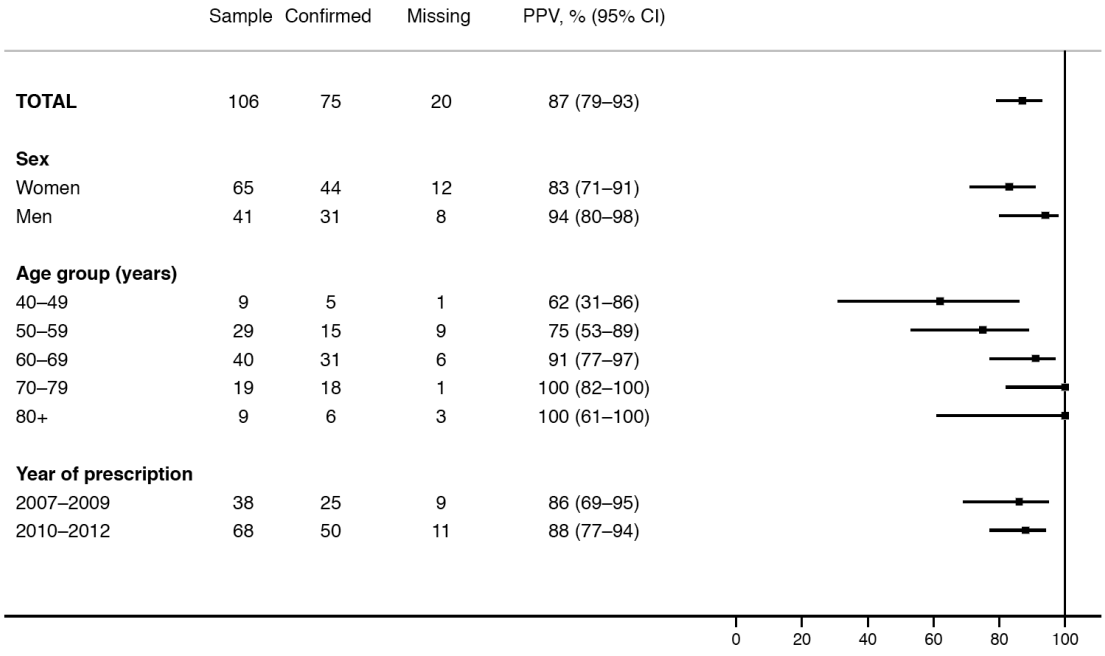
We obtained informed consent from the patient in the case vignette. The Danish Data Protection Agency approved use of the Danish data sources. Approval by an ethical review board or informed consent was not legally required for use of non-anonymized registry data. However, for the validation study, we specifically obtained approval by the Danish Health and Medicines Authorities, the Committee of Multipractice Studies in General Practice, and the steering committee for the health information system for the Central Denmark Region. The UK studies were approved by the CPRD Independent Scientific Advisory Committee and the London School of Hygiene and Tropical Medicine Ethics Committee.

4. Results

4.1 Validation in general practice (study I)

Among the 10 invited practices, one declined to participate in the validation study. From the remaining practices, we randomly sampled 176 patients with a first-time zoster prescription. We were unable to identify the indication for 34 of the patients, as they had never been registered with the general practice that had issued the prescription. Based on data for the remaining 142 patients, we estimated a PPV of 58% (95% CI: 50%–66%) for the broad algorithm. The PPV increased to 87% (95% CI: 79%–93%) when considering zoster-specific prescriptions only (Figure 6). Although the sensitivity was 90% (95% CI: 82%–95%) compared directly with the broad algorithm, we weighed specificity higher and therefore based our final algorithm on the zoster-specific definition, supplemented with hospital-based diagnoses.

Figure 6. Validity of zoster-specific prescription



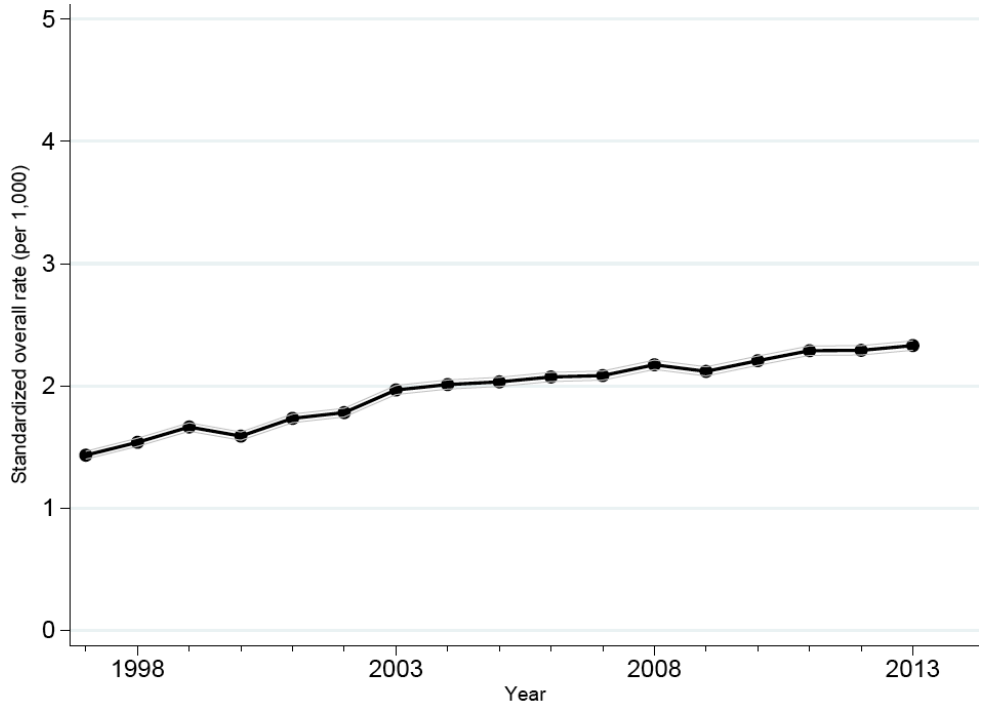
4.2 Occurrence of herpes zoster (study I)

The crude rate of zoster, as estimated by our algorithm, was 4.17 per 1000 person-years. The rates increased approximately linearly with age and were 2.15, 2.70, 4.22, 5.71, 7.34, and 8.45 per 1000 person-years at ages 40, 50, 60, 70, 80, and 90 years. Rates were higher in women than in men. Our estimates were consistent with—albeit in the lower range—of that observed in other European countries (Figure 3 – section 2.6). The rate of first-time hospitalizations with zoster as a primary diagnosis or as any diagnosis was also in agreement with previous studies.

In total, 3.5% of all 189,025 persons identified with zoster had been diagnosed during an admission. On average, 9360 persons aged 50 years or older were diagnosed with zoster annually, among whom 8.20%

had codes for severe immunosuppression. The overall age-standardized zoster rate increased from 1.4 (95% CI: 1.4–1.5) per 1000 person-years in 1997 to 2.3 (95% CI: 2.3–2.4) per 1000 person-years in 2013 (Figure 7). The increase was driven by a change in the prescription rate and was observed in all subgroups of age and sex. While median age remained stable at 64 to 66 years during the study period, prevalence of most risk factors in study I (except SLE and oral GCs) increased among zoster patients by a factor of 1.19 to 3.65.

Figure 7. Age-standardized rates of herpes zoster (95% confidence intervals), Denmark, 1997–2013



4.3 Risk factors for herpes zoster

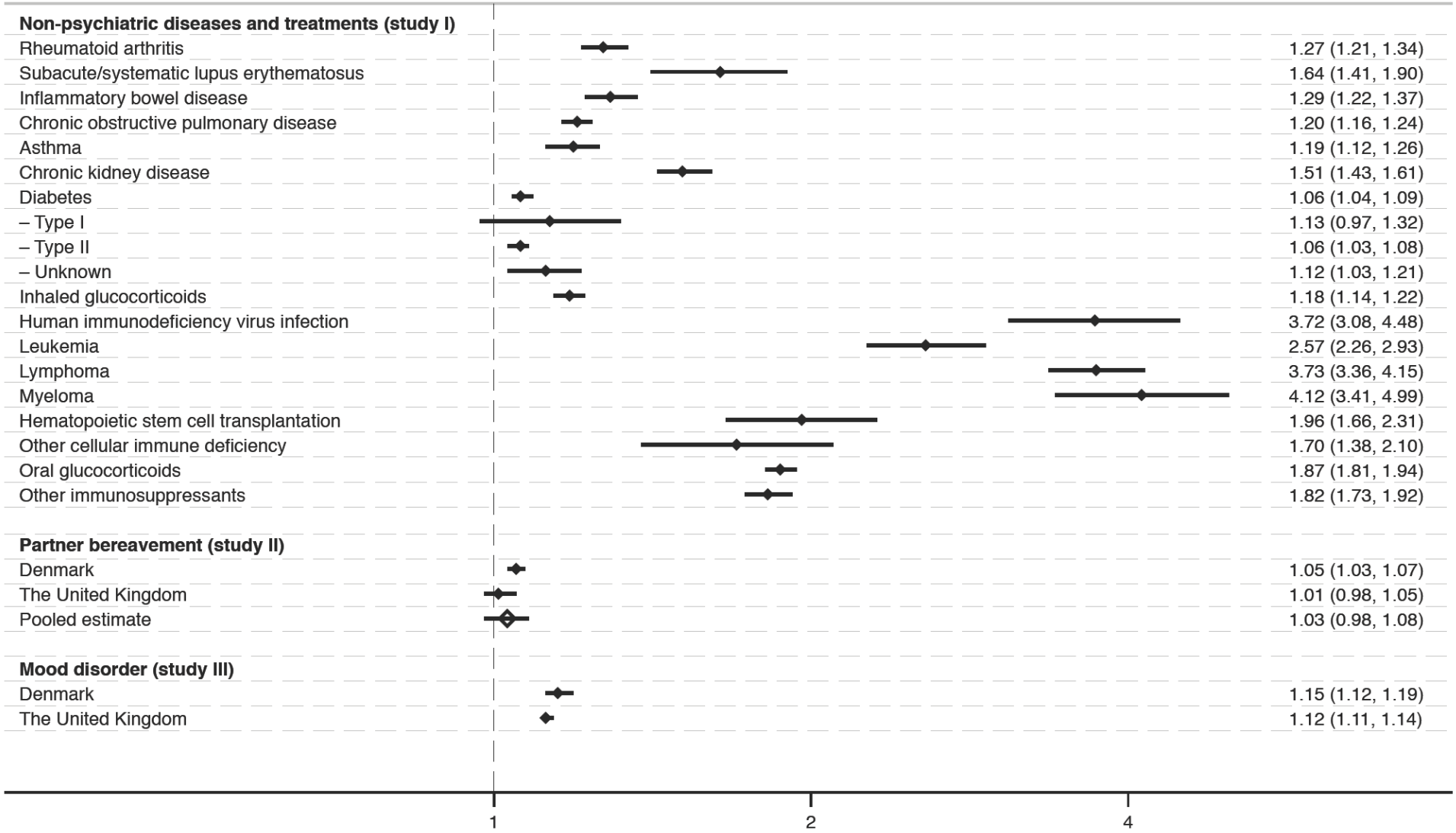
Fully adjusted ORs for each risk factor of interest in this thesis are shown in Figure 8.

4.3.1 Non-psychiatric diseases and treatments (study I)

We observed the highest ORs for factors associated with severe immunosuppression, varying from 1.70 for 'other immunosuppressive diseases' to 4.12 for myeloma (Figure 8). We also detected substantially increased risks for the other factors, including inhaled GCs. The lowest OR was 1.06 for type II diabetes. Comparison of the different logistic regression models for each risk factor is shown in Table 2 of paper I. For each exposure of interest, we observed attenuation in ORs when adjusting for the other chronic diseases. Furthermore, inclusion of inhaled GCs, oral GCs, and other immunosuppressants in the models resulted in reduced ORs for exposures that are indications for these drugs.

Hospital-based diagnoses of zoster were more strongly associated with the exposures. The case population identified in this setting also comprised older patients and more men (median age 72 years; 41.7% men) than those identified in the community (median age 60 years; 36.5% men).

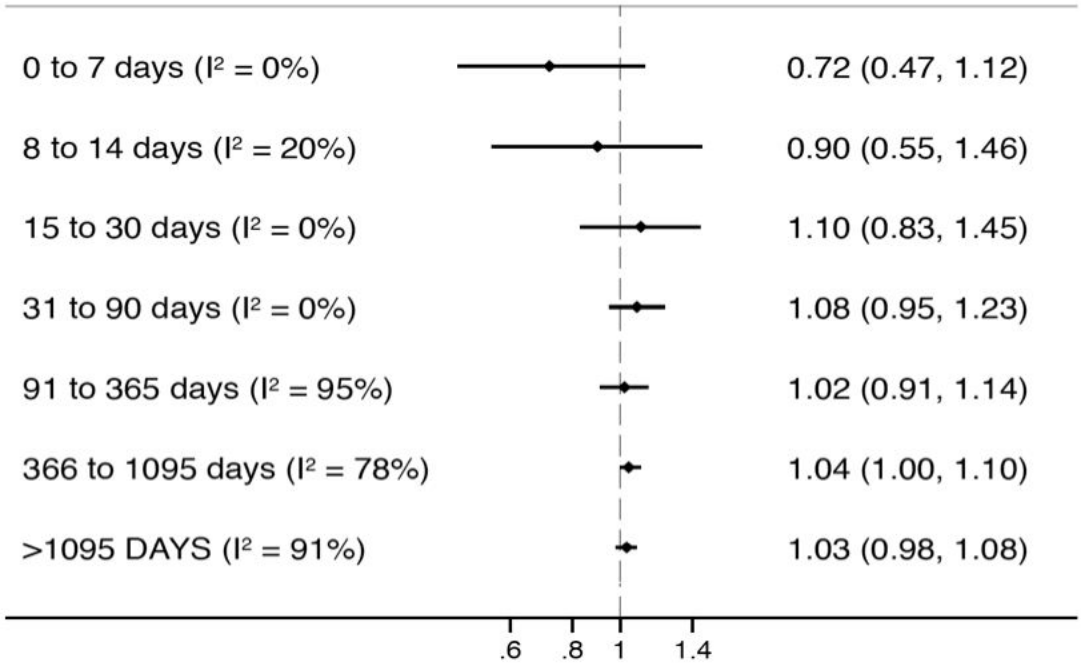
Figure 8. Forest plot of adjusted odds ratios with 99% confidence intervals for the association between exposures of interest and zoster



4.3.2 Partner bereavement (study II)

As the magnitude and direction of the adjusted ORs for previous partner bereavement were comparable in Denmark and the UK, we pooled the estimates despite substantial statistical heterogeneity (I^2 statistics >50%) for some exposure windows. The pooled adjusted OR was 1.03 (99% CI: 0.98–1.08) for any previous partner bereavement (Figure 8). We observed no substantial increase in relative risk of zoster in analyses considering time since the loss (Figure 9). The findings were consistent in subgroups defined by partner's risk of death, age, sex, and recent records of depression/anxiety, as well as in the sensitivity analyses.

Figure 9. Pooled adjusted odds ratios (99% confidence intervals) for the association between bereavement and zoster, by timing



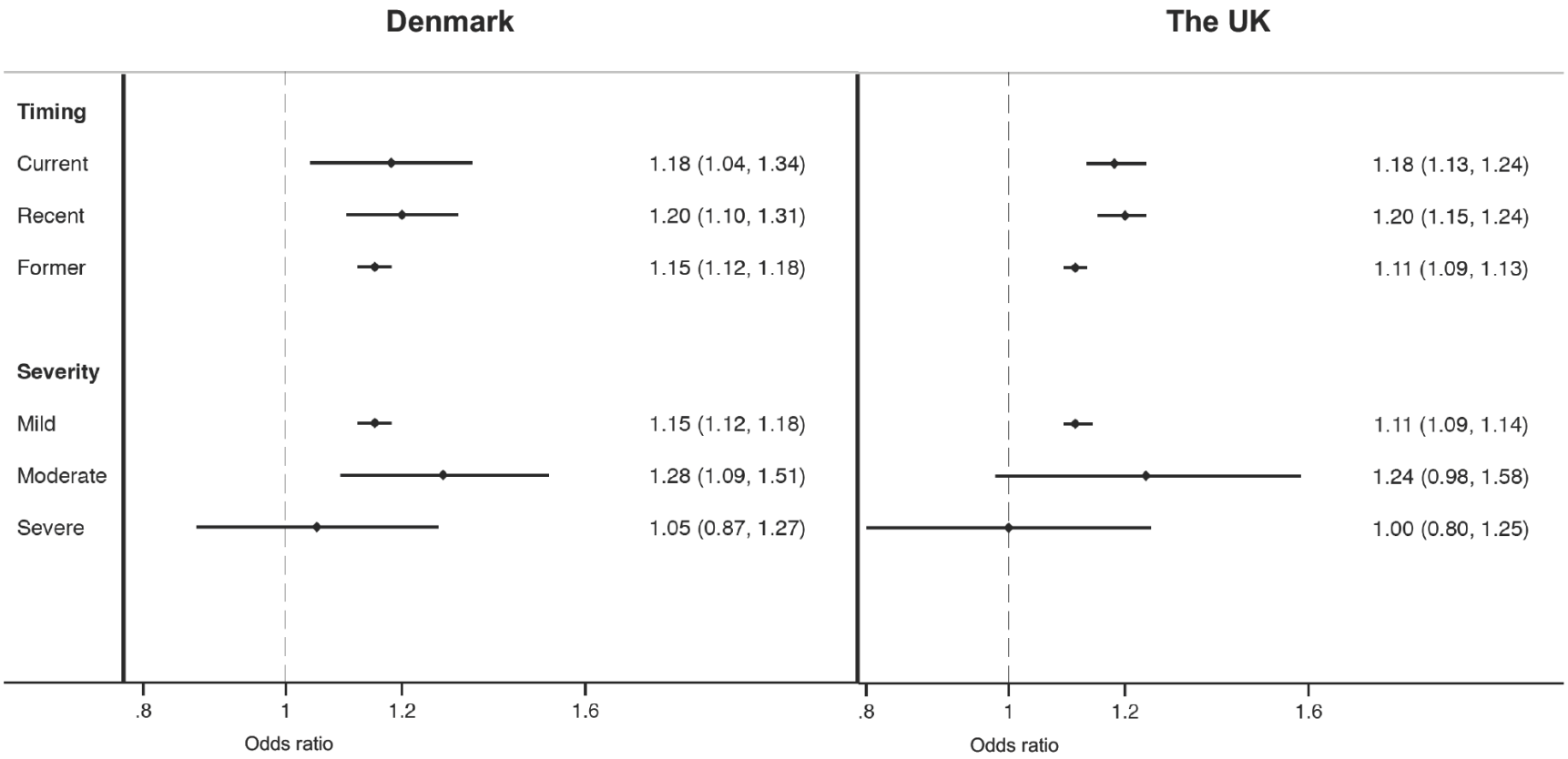
4.3.3 Mood disorders (study III)

Although record of previous mood disorder was overall 4–5 times less prevalent in Denmark than in the UK, ORs for the association with zoster were similar: 1.15 (99% CI: 1.12–1.19) in Denmark and 1.12 (99% CI: 1.11–1.14) in the UK (Figure 8). The ORs were increased for all subtypes of mood disorder, with the highest estimates observed for anxiety and severe stress and adjustment disorder in Denmark.

Analyses according to timing, suggested that the relative risk remained increased even one year after most recent healthcare contact for mood disorder (Figure 10). The findings for current mood disorders were driven by increased ORs for women, and in the UK, we also found ORs decreasing with increasing age (Figure 2 in paper III). When including antidepressants as a proxy for mood disorder in Denmark, a similar age-dependency was observed and the overall OR increased to 1.26 (99% CI: 1.24–1.28).

Analyses according to severity suggested that severe mood disorders were associated with no or only slightly increased ORs (Figure 10). As this finding was against our expectations, we performed *post hoc* analyses to explore potential biases. In particular, we suspected that the low ORs for severe disease were attributable to underascertainment of zoster diagnosed during readmission or follow-up visit at a psychiatric clinic after admission for severe mood disorder. Zoster diagnosed in this setting may be recorded as a secondary diagnosis, which would have resulted in underestimates when restricted to primary hospital diagnoses. Indeed, after repeated analyses with inclusion of secondary hospital diagnoses of zoster in our case definition, the Danish estimates for severe disease increased to 1.12 (99% CI: 0.93–1.35) in the main definition and to 1.19 (99% CI: 0.98–1.43) when also excluding antidepressant users from the reference group. In the UK, the adjusted OR similarly increased to 1.16 (99% CI: 0.94–1.43) for severe mood disorders, and the difference in estimates for current mood disorder for men (1.25; 99% CI: 1.13–1.37) and women (1.29; 99% CI: 1.22–1.36) disappeared.

Figure 10. Adjusted odds ratios with 99% confidence intervals for the association between mood disorders and zoster, by timing and severity



5. Discussion

We have developed a valid tool for identifying incident zoster based on prescriptions for antivirals at recommended doses for zoster and diagnoses from the hospital-based setting. Medical record review confirmed zoster in 87% of patients identified by a zoster-specific antiviral prescription. We have shown that zoster is a common disease among persons aged 50 years or older in Denmark and that rates increase markedly with age, are higher in women, and are potentially on the rise. We observed a 1.7- to 3.7-fold increased relative risk of zoster in persons with severe immunosuppressive factors (*e.g.*, hematological malignancy), which are considered contraindications for vaccination with Zostavax. However, we also found up to 64% increased rates associated with other chronic conditions, such as autoimmune diseases, CKD, asthma, and COPD. While partner bereavement, a proxy for extreme stress, was not associated with zoster, persons with mood disorders had a 15–20% increased relative risk compared with persons without mood disorders.

5.1 Comparison with existing literature

5.1.1 Occurrence of herpes zoster (study I)

The age-specific rates of zoster in the Danish general population, as estimated by our algorithm, are higher than those reported by Christensen and Nørrelund in 1985.[47] Increased population longevity[276] and advances in immunomodulatory therapy (*e.g.*, biologicals)[72] may have caused a change in the epidemiology of zoster since that older study. As described in the background chapter (section 2.6.1), underreporting from participating practices and exclusion of immune-incompetent patients may have resulted in underestimates in that study. Comparison with the other Danish study by Østergaard *et al.*[49] is difficult because they estimated the age-specific prevalence of zoster whereas we estimated rates. Nevertheless, they also found a predominance of women (OR 1.63; 95% CI: 1.16–2.30) and an increased OR of self-reported zoster with age. The decreased ORs associated with lung disease and diabetes in their study are, however, controversial and could suggest selection bias from restricting to volunteers from organized influenza campaigns.

Our study most likely demonstrates a conservative estimate of the rate of zoster in Denmark, as our algorithm does not capture patients who did not redeem an antiviral medication in general practice. It is therefore not surprising that the Danish rates are in the lower range of that reported across Europe (Figure 3).[34-43] Of interest, our algorithm yields rates similar to Swiss sentinel data[39]; however, this comparison should be viewed in light of the secular increase in rates of zoster because our data from Denmark were more recent than those used in the Swiss study.[39] Rates based on sentinel data from Belgium,[38] the Netherlands,[37] and France[40] are in line with routinely collected data from Sweden[34] and the UK.[35]

The particularly high rates observed in Germany may have several explanations. First, universal varicella vaccination was implemented in Germany on a national level in 2004,[23] which hypothetically could increase zoster rates through reduced exogenous boosting.[61] Rates are also quite high in Madrid, Spain, where a regional vaccination program was effective during 2006–2013. However, it seems implausible that

reduced exogenous boosting due to vaccination would have such a pronounced impact on occurrence of zoster within only one to two years after implementation in Germany, and the standardized rates remained stable from 2006 (5.3 per 1000 person-years) to 2009 (5.5 per 1000 person-years).[36] Furthermore, regional vaccination programs have been effective in regions that contributed data from Italy (since 2005 in Veneto and 2010 in Puglia and Toscana)[41] where the rates are comparable with those observed before implementation[55] and in other European countries (Figure 3). A second explanation for the higher rates in Germany[36] and Spain[42] is that the studies did not differentiate entirely between zoster episodes (healthcare contacts) and first-time diagnoses, which may have inflated estimates by inclusion of recurrences and repeated contacts for zoster neuralgia. Finally, the prevalence of risk factors for zoster may differ across Europe. Although prevalence of immune incompetence was similar in Denmark and Germany (9%),[36] definitions differed and other risk factors might play a role.

The almost linear increase in rates of zoster with age is seen in many countries. In Germany[36] and Italy,[41] reported rates level off or even decrease after age 80 years, which may be explained by imprecision or underascertainment in the elderly population, *e.g.*, due to frailty. The Danish National Prescription Registry includes prescriptions dispensed for persons living in communal establishments, including nursing homes, which presumably limits this potential bias in our data.[253] The difference in rates among women and men in Denmark is also consistent with other countries.[46]

The temporal trends estimated by our algorithm are overall consistent with data from other European countries, North America, Australia, and Asia, which also show increasing rates (reviewed in[5]). It has been suggested that this trend is caused by decreased circulation of wild-type VZV—and hence reduced boosting of VZV-specific immunity—in countries with childhood varicella vaccination programs.[61] However, the increase in rates in Denmark and other countries where no childhood vaccination programs have been implemented does not provide support for this hypothesis.[5] Furthermore, in countries with childhood vaccination programs, an increase started even before implementation.[5] In our study and a recent US study,[277] a concurrent increase in immunosuppressive factors was observed among zoster patients, suggesting that reduced immune competence in the general population could explain part of the increase. However, we cannot rule out confounding from changes in public awareness, access to healthcare, and in our study, doctors' prescribing of antiviral medications (driven by, *e.g.*, price changes).

5.1.2 Risk factors (studies I–III)

To the best of our knowledge, our studies on zoster risk factors are the largest published to date. The relative risk estimates for risk factors examined in study I are remarkably similar to those found in the UK data (Figure 4, paper I). Data are also in line with other studies, although we note that estimates are generally more pronounced in studies using primary data collection, in particular with case–control designs (Table 3). We not only confirm severe immunosuppressive conditions as risk factors for zoster but also demonstrate evidence supporting other chronic diseases as risk factors. The increased risks associated with RA, SLE, and IBD in unadjusted (sex- and age-matched) models were mediated only partly through immunosuppressive

treatments and multimorbidity, which is consistent with the hypothesis that immune dysregulation in autoimmune diseases leads to impaired VZV-CMI. The association between type I diabetes and zoster may have the same explanation, but epidemiological studies are controversial (Table 3).[35,100,203,204] Unfortunately, most previous studies did not differentiate between types of diabetes. It is therefore likely that their estimates were driven by the more frequent type II diabetes, which has a less clear autoimmune component and no substantial association with zoster in our data. The findings for CKD,[35,87,126,195-197] as well as asthma[35,90,92,100,183] and COPD,[35,87,92,116,185] are in line with previous large studies. Data on inhaled GCs are sparser, consisting of two CPRD studies.[35,189] Considering the general CPRD population, the ORs for inhaled GCs are very similar ours[35] whereas a study among regular users of respiratory medications found no association.[189] The latter may suggest residual confounding by indication from obstructive lung disease in studies in the general population.

In study I, we found higher ORs for risk factors among patients with hospital contact for zoster. This result could suggest a higher risk of complications, a lower threshold for referral, and/or coincidental diagnosis of zoster during routine hospital-based follow-up in, *e.g.*, immunosuppressed patients. These possibilities should be considered when interpreting results from hospital-based studies on zoster.

The association between depression and risk of zoster is in agreement with previous studies using routinely collected healthcare data (Table 4).[35,100,116,126,222,223] Furthermore, we extend this finding to anxiety and severe stress and adjustment disorders, which were not included in previous studies or were mixed together with codes for depression or other psychiatric conditions. However, the hypothesis of psychological stress as a biological explanation for these findings is challenged by the lack of an association between partner bereavement and zoster in study II. Similarly, no association was found between unexpected spousal health events and zoster in a self-controlled case-series from the US.[224] As we lacked direct measures of immune function, we can only speculate about the mechanisms explaining these inconsistencies. Psychological stress is difficult to measure because stress depends on the type and duration of the stressor, as well as personal coping mechanisms.[214] Although bereavement is considered extremely stressful, grief is variable.[278,279] Thus, while most people adjust without professional psychological intervention, 9% go on to develop complicated grief (*i.e.*, grief that deviates from the cultural and societal norm).[279] The final allostatic load, including the severity of immunosuppression, may depend on the presence of such reactions, as suggested by an association between depressive symptoms and reduced immune function in women experiencing negative life events.[217,218] It is possible that our bereavement study did not succeed in detecting immunosuppressive effects of such complicated grief while the more chronic and 'pathological' stress in patients with mood disorder resulted in a clinically evident risk of VZV reactivation. Unfortunately, we did not have data on perceived stress, which may have been a better measure of allostatic load, as it reflects an individual's general ability to cope or unwind in everyday life. This difference could explain why previous smaller studies considering a wide range of different self-reported negative life events found an increased risk of zoster[77,78,89,225] whereas we did not. However, risk of, *e.g.*, recall and selection bias in those studies (section 2.7.3) calls into question the causality of their findings. Alternative explanations to psychological

stress could also be involved for mood disorders. We had expected to find the highest estimates for current and severe mood disorder but observed no substantial difference. Shared biological mechanisms for depression and infections thus also could have played a role in study III. For example, it has been suggested that immune dysregulation in autoimmune diseases and severe infections is linked to the development of mental illness.[280] The methodological limitations of our own studies should also be considered and are discussed below.

5.2 Methodological considerations

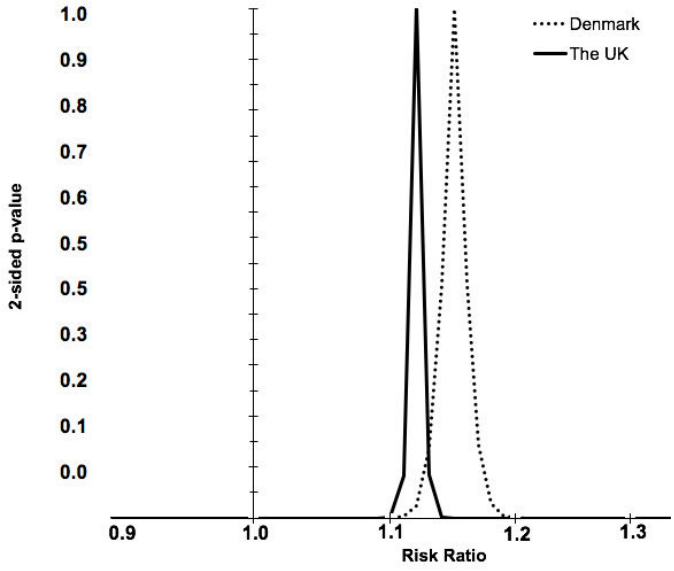
The goal of an epidemiological study is to provide accurate estimates of disease occurrence or the effect of an exposure on the outcome. However, errors in estimation are inevitable. The total error of an effect estimate parses into random error and systematic error.[281] The main sources of the latter are selection bias, information bias, and confounding.[281] Critical appraisal of any study should involve an assessment of each of these potential threats to internal validity. The following sections address potential sources of error in our studies. Finally, an important and related issue, generalizability, is discussed.

5.2.1 Random error (chance)

Random error, or chance, relates to statistical precision. According to good epidemiological practice, we used the width of the confidence intervals to quantify precision.[282,283] We did not use p-values (or locations of CI boundaries) so as to avoid fostering frequent misrepresentations in which inferences are reduced to dichotomy based on statistical rather than clinical significance. The statistical confidence levels in our studies (alpha-level 0.01 and 0.05) are thus also arbitrary.

The overall precision in our studies was high, as illustrated by the probability functions in Figure 11, where overall estimates from study III are used as the example. However, the statistical precision of our estimates should not be overemphasized. First, estimates from subgroup analyses were less precise and should be interpreted with caution. Second, standard errors derived from conventional statistical methods are computed based on the assumptions that all errors in estimation are random (*i.e.*, without bias) and that models are correctly specified (*e.g.*, no heterogeneity).[284] As these assumptions go beyond what is probable for most studies, including observational studies like ours, the confidence intervals illustrate merely the

Figure 11. P-value function for odds ratios for any previous mood disorder in study III



minimum statistical uncertainty.[284] Finally, given the size of our studies, random error contributes relatively little to the total error. In recognition of these precautions, we will leave the issue of chance and shift the attention towards the potential sources of systematic error.

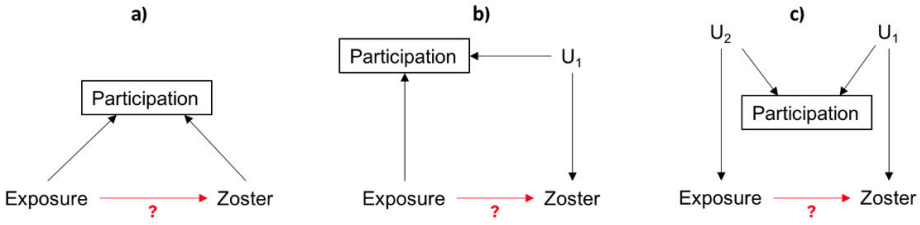
5.2.2 Selection bias

Selection bias refers to a situation in which the measured study estimate deviates from the true association of interest because persons included in the study (or the registry) are not representative of the target population in that specific aspect.[281] In other words, the association thus differs between participants and non-participants. In cohort studies, selection bias also occurs if continued participation depends on exposure and risk of outcome (differential loss to follow-up or competing risks).

In our validation study, selection bias may have been introduced by design or by invited practitioners ('self-selection bias') if factors related to inclusion are also related to validity. However, we find it unlikely that non-participating practices treat zoster and other herpes infections differently. Although this inference is not verifiable, it is supported by similar demographics for patients prescribed antivirals by the included and excluded practices. Unfortunately, we could not directly compare the prescription rates for practices because we had no data on denominators and demographic composition of the catchment populations. Another potential source of selection bias in the validation study is missing indication for 19% of prescriptions. These patients likely presented with acute herpes infections at out-of-hours services, and it is difficult to know if such infections would be treated differently. A worst-case scenario analysis where persons who were dispensed a zoster-specific prescription and had missing record are assumed not to have zoster yields a bias-adjusted PPV of 71% (95% CI: 61%–79%). In a best-case scenario, the PPV is 90% (95% CI: 82%–94%).

Figure 12 shows diagrams for hypothetical mechanisms that may lead to selection bias in analytical studies, such as in studies I–III of zoster risk factors. The situation in Figure 12a can arise if the outcome in a study affects participation either because of self-selection (*e.g.*, in cross-sectional or retrospective case–control studies) or because the control group in a case–control study does not appropriately reflect the exposure prevalence in the source population (Berksonian bias).[250] This scenario is unlikely in our studies because we used prospectively collected data and population controls. Selection bias may also arise if a predictor or risk factor ('U1') for zoster affects participation, which at the same time is affected by exposure (Figure 12b) or shares a common cause/ancestor ('U2') with exposure (Figure 12c). Our studies were

Figure 12. Directed acyclic graphs for examples of selection bias



conducted in well-defined populations with universal access to healthcare, which limits the role of financial or other social barriers as determinants ('U1', 'U2') of inclusion. Furthermore, scenarios 12b and 12c can be thought of as confounding because adjustment for U_1 and/or U_2 will close the biasing ('backdoor') pathway between the proposed risk factor ('exposure') and zoster. The negligible effect of adjustment for proxies of socioeconomic status in studies II and III is therefore reassuring.

5.2.3 Information bias

Information bias arises because of mismeasurement of study variables.[281] The direction and magnitude of the resulting bias in effects measures depend on whether or not the error depends on the actual value of that variable or other variables of interest (differential vs. non-differential misclassification) or the errors in measuring other study variables (dependent vs. non-dependent misclassification).[281] Potential misclassification of outcome (zoster) and exposures in our studies is discussed below. Covariable misclassification relates to the topic of residual confounding and will be addressed in that context.

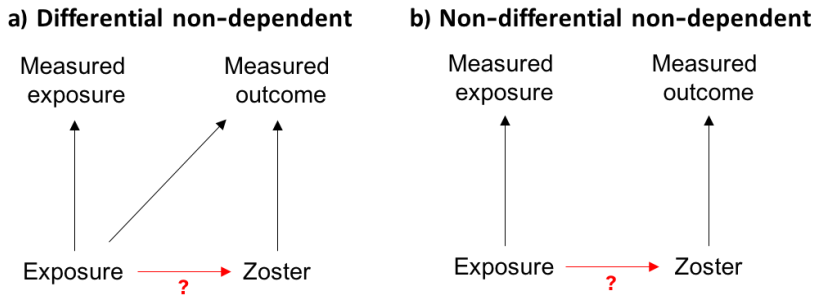
Misclassification of herpes zoster

Correct classification of zoster depends on several factors, including patient healthcare seeking, quality of the clinical diagnosis, prescribed treatment (in the Danish data), and reporting to the registries.
Overall, the data quality can be characterized by the validity and completeness of our algorithms.[285] Validity describes whether the algorithm identifies what it is supposed to (*i.e.*, patients with zoster). The largest threat to validity in the Danish data is the use of antiviral prescriptions to identify zoster treated outside the hospital-based setting. We therefore specifically examined the PPV of this proxy in paper I and found high validity of zoster-specific prescriptions (87%). However, a slight overestimate due to misdiagnosis in the medical record (reference standard) is possible.[286-288] Furthermore, we chose a more inclusive and potentially less specific definition of zoster-specific doses of valacyclovir and famciclovir, but these appeared infrequently in the validation sample. The validity of zoster in the UK data and the Danish National Patient Registry is unknown, but our most qualified guess is a PPV of at least 90% based on validation studies of physician-based diagnoses in other settings.[286-288]

Completeness refers to the proportion of true zoster patients captured by our algorithm. The lack of a suitable reference standard prevented us from estimating measures of completeness (sensitivity). However, the comparison of age-specific rates in Figure 3 gives an indirect impression of completeness. The UK rates are in the midrange of that found in other countries. The Danish algorithm seems to have a sensitivity of 70%–80% compared to Sweden,[34] which is likely the best reference given the homogeneity of the Scandinavian healthcare systems and populations. Multiple factors may explain this incompleteness. First, immune-competent patients who present to their physician late or who are aged <50 years and have mild truncal rash may not receive antiviral therapy.[29] One UK study found that 65% and 93% of adults with zoster presented within 72 hours and 7 days after rash onset.[94] However, extrapolation of data on prescription practices between countries may be inappropriate, as suggested by the large European variation in

proportions of zoster patients who are issued an antiviral (50 to >90%).[36,38,289-291] Second, patients who never dispensed prescribed antiviral therapy were omitted. Third, restriction to zoster-specific prescription resulted in exclusion of 10% of treated patients who received low doses of antivirals. Dose reduction is mainly recommended for patients with reduced kidney function,[29] and it is therefore surprising that ORs for CKD were not lower than in previous studies. Fourth, in both Denmark and the UK, patients with zoster who never sought care were not included. Survey data suggest that this proportion is small (<10%),[49,292] likely owing to the extensive rash and pain. Finally, we missed zoster patients who were misdiagnosed with other diseases, hospital-based cases who were not reported to the hospital registries, and UK patients who were diagnosed in outpatient clinics and hospitals not captured by the HES. This absence likely has little consequence for our estimates overall because hospital-based diagnoses constitute a minor proportion of all zoster cases.

Figure 13. Directed acyclic graphs for outcome misclassification



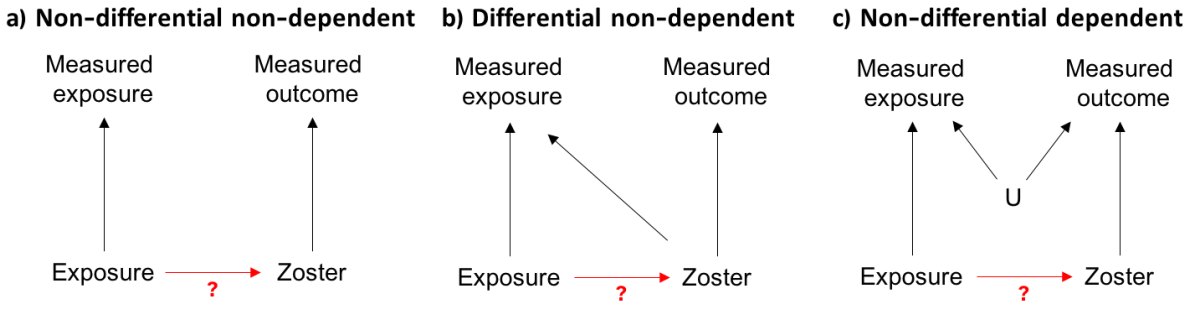
Incompleteness of our algorithm likely outweighs the number of false-positive cases, thus leading to underestimation of the occurrence of zoster in Denmark in study I. The potential bias is, however, less predictable for risk factor analyses. Although specificity unlikely depends on exposure status, completeness may be differential because of unequal medical attention of exposed and unexposed groups (Figure 13a). Most of the risk factors studied are associated with frequent medical attendance, which could overestimate associated risks of zoster (ascertainment bias). People with, *e.g.*, mood disorder may also seek care for conditions such as zoster more frequently than healthy persons. However, such bias could also have acted in the other direction in studies II and III. In the midst of the psychological aspects of partner loss, many practical arrangements need to be managed. Delayed healthcare contact in this stressful period may have caused underascertainment of zoster, consistent with the transient (albeit statistically imprecise) decrease in relative risk within 14 days after bereavement. Similarly, loss of energy or avoidance symptoms may have prevented healthcare seeking for zoster in persons with mood disorder. We anticipated a larger degree of bias in the Danish data where most zoster patients were identified by antiviral treatment, which depends on timely healthcare seeking. The remarkable similarity with UK estimates thus provides some reassurance that differential misclassification is not a major issue and gives further credence to the Danish algorithm. Further evidence against ascertainment bias is provided by previously published analyses of the UK data that showed that the OR for epilepsy, a negative control that requires regular healthcare contact but is not suspected to

increase risk of zoster, was below that observed for most exposures identified as risk factors in this thesis (OR 1.06; 99% CI: 0.97–1.15).[35] Based on these observations, non-differential misclassification (Figure 13b) seems most likely for our data, which provides justification for our choice of the more stringent but less complete algorithm in Denmark, where bias due to low sensitivity is limited when specificity is high.[281]

Misclassification of risk factors

We assessed a large number of risk factors in this thesis. In study I, we investigated whether the secular increase in rates of zoster was paralleled by an increase in prevalence of risk factors among persons with zoster. It is possible that the latter is explained by increased ascertainment (completeness) of risk factors in the Danish National Patient Registry over time because of changes in diagnostic procedures and classifications, coding practices, or administrative changes.[241] For example, hospital treatment codes (*e.g.*, for immune-modulating therapy) were introduced in 1999, and reimbursement of hospitals based on diagnoses submitted to the Patient Registry began in 2002.[241] Nevertheless, the decreasing prevalence in use of oral GCs and increase in other immunosuppressants is in line with gross sales statistics for the Danish population in general.[249]

Figure 14. Directed acyclic graphs for exposure misclassification



Misclassification of other risk factors is most likely non-differential in our studies (Figure 14a) and depends on factors such as quality of the clinical diagnosis and reporting to the registries. Data were collected prospectively, which avoids the recall bias or reverse causation that occurs when outcome affects the exposure measurement (Figure 14b). Similarly, dependent errors in exposure and outcome measurements are unlikely (Figure 14c).

Non-differential non-dependent misclassification of a dichotomous exposure is expected to cause bias to the null (or beyond if sensitivity and specificity sum up to <1.0). This situation is thus likely for many of our risk factors in study I. Validity is high (PPV 80%–100%) for most conditions, except for diagnosis codes for asthma (PPV 65% vs. self-report) and RA (PPV 59%–75% vs. medical record review).[241] Because hospitals are reimbursed for delivered care, we expect also high completeness of hospital-based diagnoses and treatments. However, some conditions are treated mainly in general practice, which reduces overall sensitivity.[241] We tried to mitigate this by incorporating prescription data in our definitions when appropriate.

Although the Danish National Prescription Registry is considered complete[253] and none of the included medications are available over-the-counter, hospital-based immunosuppressive therapy may be incompletely registered. In addition, non-adherence should be considered. Misclassification of diabetes type, which was defined based on treatment and age at first diabetes record, is also possible.

In study II, we intended to measure severe psychological stress by partner bereavement. Potential misclassification in this study is twofold, as it depends on (i) correct identification of partner death and (ii) whether experiencing partner death resulted in severe stress. Variables used to identify partner death (*e.g.*, address, kinship, and vital status) in Denmark are considered of high quality.[252] The identification of partners was probably less complete in the UK, as partners had to be registered with the same GP. Nevertheless, distribution of exposure was very similar in Denmark and the UK and analyses were unchanged when restricting the comparison persons in a couple. Partner bereavement affects most persons gravely, and we thus believe that it is a valid measure of stress. However, some misclassification of onset and severity of psychological stress is likely to have occurred in analyses according to timing and risk of partner death because both may depend on the cause and expectedness of the loss. (*e.g.*, long-term dementia vs. sudden cardiac death). Misclassification of some family members as partners is considered of little concern as the death is still likely to represent significant bereavement in a person's life. Furthermore, although some persons in the non-bereaved group may have been psychologically distressed for other reasons, it is unlikely that their distress would consistently center around the same time when the exposed group was bereaved. Finally, the algorithms have previously been used in both Denmark and the UK, showing increased risks for non-infectious diseases and death, particularly in the months after bereavement.[267-269,293]

Non-differential misclassification probably caused us to underestimate the association between mood disorders and zoster in study III. Compared with strict criteria applied to medical records, PPV of diagnosis codes for severe stress and adjustment disorders in the Danish Hospital Registries varies from 58% for acute stress reaction to 94% for adjustment disorder.[294] For single depressive episodes, the PPV is 75% in comparison with interview.[295] However, the overall validity of mood disorder is likely higher in our study because some of the misclassification occurs between the subtypes.[294,295] The validity of diagnoses in the UK is unknown, and diagnoses from psychiatric hospital departments and outpatient specialty clinics were largely unavailable.

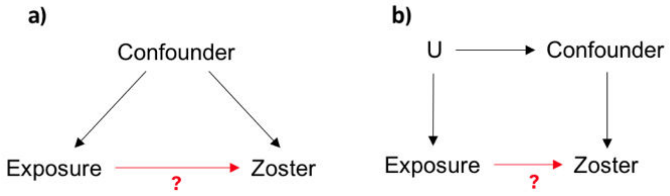
Although specificity of non-psychiatric physicians' recognition of depression is high (84%),[296] validity was likely affected by inclusion of codes for symptoms of depression in the UK. On the other hand, completeness was much lower in Denmark where we had no data on general practice. The misclassification introduced in this case was demonstrated by the increase in estimates upon inclusion of antidepressants as a proxy for diagnosis in Danish primary care. It should also be noted that misclassification may vary by other characteristics and could thus explain the lower estimates observed in the oldest subjects[297] and in men.[298] However, *post hoc* analyses suggested that poor ascertainment of zoster in persons with severe mood disorder explains the gender difference. The lower ORs in the oldest age group may also be explained by a

high prevalence of other risk factors for zoster, which overwhelm the relative effect of mood disorders. Indeed, the absolute increase in rate of zoster was similar across age.

5.2.4 Confounding

Confounding is the confusion of effects that occurs when a predictor of the outcome is unevenly distributed between exposure groups because it is a direct or indirect cause of the exposure (Figure 15a) or shares an ancestor with the exposure (Figure 15b).[281] Factors on the pathway of interest leading from exposure to outcome (mediators) are not considered confounders. Confounders can be controlled for by design (*e.g.*, restriction or matching) and by statistical analyses (*e.g.*, standardization, stratification, or adjustment).

Figure 15. Directed acyclic graphs for confounding



We controlled for a large number of potential risk factors. Exposures in study I served also as potential confounders, and misclassification (discussed above) would in this context have led to residual confounding. Residual confounding by treatments may thus explain part of the increase in risk associated with immune-mediated conditions in the fully adjusted model. Conversely, confounding by indication may contribute to some of the risk associated with the treatments, as we lacked clinical data on severity. Regardless of the mechanisms, patients with immune-mediated conditions seem to have an increased risk of zoster. Confounding by, *e.g.*, smoking and alcohol consumption is also possible in study I, although data on lifestyle factors and risk of zoster are controversial (Table 2). In studies II and III, unadjusted and adjusted estimates were similar, suggesting that residual confounding is limited. The inclusion of data from both Denmark and the UK also enabled us to explore confounding by different factors and suggested that lifestyle factors and socioeconomic status also played limited roles. Nevertheless, residual (or unmeasured) confounding from, *e.g.*, lifestyle associated with mood disorders and zoster may have occurred.

Other sources of unmeasured confounding are also possible. The secular changes in rates of zoster in paper I may have been at least partly confounded by changes in public awareness, healthcare access, or doctors' prescribing of antiviral medications for zoster. Confounding by genetic factors or ethnicity may also have occurred in the studies. For example, persons with South Asian heritage have a greater risk of type 2 diabetes[299] but a lower risk of zoster, which may have caused an underestimate of the association for this condition.[60] As the Danish population is predominantly of Northern European ancestry, we expect only minor differences in prevalence of other ethnicities and a consequently limited degree of confounding. Confounding by yet unidentified risk factors for zoster cannot be ruled out.

5.2.5 Generalizability

Generalizability means that a study's results apply in other settings or populations and is predicated on good internal validity.[281] The validation study and comparison of estimates for risk factors for zoster with routinely collected data on diagnoses of zoster suggests that our algorithm performs well in Denmark. However, the validity and completeness of the algorithm to other settings may not be generalizable if there are large differences in prescribing of antivirals for herpes simplex and zoster or quality of prescription data. Generalizability of the algorithm *in* other studies may also depend on the objective. Because the algorithm captures mainly treated patients (*i.e.*, the optimal scenario), studies designed to investigate direct complications may underestimate the risk associated with zoster, assuming antiviral treatment is effective. This difference has previously been demonstrated in studies on the risk of stroke after zoster.[300]

Assuming that systematic and random error is negligible, comparison of the ORs for risk factors in Denmark and the UK provides evidence in favor of their generalizability to similar populations. We note that representativeness is not a prerequisite for generalizability.[281,283] However, a different prevalence of effect modifiers in other target populations (*e.g.*, Asian populations) may limit extrapolation. Unfortunately, we lacked data on, *e.g.,* ethnicity, which prevented stratified analyses that could be informative about applicability to non-white populations.

5.3 Main conclusions and perspectives

The WHO and the European Centre for Disease Prevention and Control have stressed a need for better understanding of the epidemiology of zoster. Although zoster is a common disease, data on its occurrence in the general population are lacking in many countries, including Denmark. Furthermore, as most known risk factors for zoster (severe immunosuppression) explain only a small proportion of cases (<10% in our material), it remains unclear why some persons develop zoster while others do not. Unfortunately, most countries do not record diagnoses of zoster routinely in the general population, which hampers studies into the epidemiology of zoster.

In this thesis, we have developed an algorithm for identifying zoster based on routinely collected healthcare data on dispensed prescriptions for systemic acyclovir, valacyclovir, and famciclovir and hospital-based diagnoses. Based on our findings, we believe that our algorithm provides a useful tool for future etiologic or prognostic epidemiologic studies on zoster. There is also a potential for use in other settings, but validation is required to ensure generalizability.

In the current work, we applied our algorithm to study the occurrence of zoster in Denmark during a 17-year period prior to marketing of Zostavax and conducted the largest studies to date on risk factors for zoster. In study I, we showed that zoster is a common disease among persons aged 50 years or older in Denmark. The rate is highest in women and increases with age and calendar time consistently with that observed in other countries. Although the higher rate among women has been noted in the past, the explanation remains unclear and warrants investigation. Furthermore, it may provide clues into unknown

gender-associated risk factors for zoster, *e.g.*, hormone levels. The potential temporal increase in rates of zoster also requires further investigation and underpins the importance of vaccine development.

The thesis also provides insights into potential causes of VZV reactivation. We confirmed and quantified the high risk of zoster associated with severe immunosuppressive conditions (use of immunosuppressant, hematological cancers, HIV, and other cellular immune deficiency), as well as RA, SLE, and IBD. We also found an increased risk associated with more controversial factors, including type I diabetes, CKD, asthma, COPD, and inhaled GCs. Physicians and patients should be aware of this risk and informed about the possibility of vaccination. These data may prove useful for vaccine policymakers. As the cost of Zostavax is high, prioritized vaccination targeted at persons with these chronic diseases may be a viable alternative to universal vaccination, especially considering that these patients were more often treated in the hospital-based setting and may have an increased risk of acute and chronic complications of zoster.[7,155,156,301,302] Effectiveness of Zostavax has been reported in patients with diabetes, kidney disease, cancer, and autoimmune conditions.[87,130,139,178,303] However, there is a dearth of data on the safety of vaccinating prior or during iatrogenic immunosuppression,[139,303,304] which was associated with high relative risk of zoster in our material. In this context, the prospects of the new subunit vaccine are far-reaching, as they bring further promise for prevention in patients with severe immunosuppression, including from non-iatrogenic causes.

Our work also adds to the growing evidence of potential negative consequences of poor mental health by showing that persons with mood disorders exhibit an increased risk of zoster. This result extends previous studies indicating that VZV-CMI and vaccine immunogenicity are reduced in patients with major depression. These findings call for investigations of vaccine efficacy or effectiveness in patients with mood disorders, including studies into the potential need for more potent vaccines and repeated administration.

Our findings for bereavement complicate the interpretation that the association between mood disorders and zoster is explained by psychological stress. Reasons for this discrepancy may be found in the level of perceived stress. Continued research into the role of psychological stress, as well as the largely unexplored effects of other unhealthy aspects of lifestyle (*e.g.*, diet), is needed.

Finally, our systematic review in study IV (presented in the introduction) suggests that zoster may be triggered by occult cancer, as patients presenting with zoster have an increased risk of cancer, especially hematological cancers. However, there are several questions that remain unanswered: What is the absolute risk of occult cancer for a patient presenting with zoster? Are there some subgroups where physicians should be particularly concerned about presence of cancer (*e.g.*, those without the presence of other provoking factors)? Is there a prognostic benefit of initiating work-up for cancer (*e.g.*, through integrated cancer pathways) in zoster patients? Which diagnostic procedures are most useful? And does the potential benefit outweigh associated physical and psychological distress? Research into these areas is needed before any changes in clinical practice can be implemented.

6. Summary

Herpes zoster is a vaccine-preventable disease caused by reactivation of the varicella zoster virus from sensory ganglia. Although it has been estimated that up to 50% of persons who survive until age 85 years will develop zoster, little is known about the burden of zoster and its risk factors. The World Health Organization and the European Centre for Disease Prevention and Control have thus stressed a need for better understanding of the epidemiology of zoster. Unfortunately, data on zoster in the general population are not available in most countries, including Denmark. In this thesis, we aimed to develop an algorithm for identifying zoster based on routinely collected prescription and hospital data and to perform epidemiological studies on the occurrence of zoster and its risk factors.

Study I was conducted using the Danish health registries. First, we undertook a validation study in general practice to evaluate whether a first-time prescription for systemic acyclovir, valacyclovir, or famciclovir can be used as a valid proxy for zoster treated outside the hospital-based setting. Through medical record review (n=86), we were able to confirm zoster among 87% (95% CI [confidence interval]: 79%–93%) persons who dispensed a prescription most compatible with recommended treatment for zoster (800 mg acyclovir in packets of 35 pills or 500 mg tablets of valacyclovir or famciclovir). We then used this definition, supplemented with diagnoses from the hospital-based setting, to study the occurrence of zoster in Denmark during 1997–2013. We identified 189,025 persons with zoster. The rates of zoster increased from 2.15 per 1000 person-years in 40-year-olds to 8.45 per 1000 person-years in 90-year-olds. Rates were higher in women than in men. The age-standardized rate increased during the study period. Approximately 3.5% of persons had zoster diagnosed during hospitalization. Compared with matched population controls (n=945,111), persons with zoster had increased odds ratios (ORs) of rheumatoid arthritis (1.27), subacute/systemic lupus erythematosus (1.64), inflammatory bowel disease (1.29), chronic obstructive pulmonary disease (1.20), asthma (1.19), chronic kidney disease (1.51), type I diabetes (1.13), and use of inhaled glucocorticoids (1.18) in multivariable conditional logistic regression analyses. As expected, ORs were particularly high for severe immunosuppression, including human immunodeficiency virus (3.72), leukemia (2.57), lymphoma (3.73), myeloma (4.12), hematopoietic stem cell transplantation (1.96), other cellular immune deficiency (1.70), and treatment with oral glucocorticoids (1.70) or other immunosuppressants (1.82). Overall, 8.2% of zoster patients were severely immunosuppressed.

In studies II and III, we examined the hypothesis that psychological stress can trigger zoster. In **study II**, we used partner bereavement as a proxy of extreme stress. In **study III**, we studied mood disorders, including depression, anxiety, and severe stress and adjustment disorder, as these conditions may be chronically stressful. We designed the studies as case–control studies in Denmark (1997–2013) and the UK (2000–2013), including over 150,000 cases of zoster each in Denmark and the UK and up to 4 times as many controls. We found no evidence of an association between partner bereavement and zoster in Denmark (OR=1.05; 99% CI: 1.03–1.07) or the UK (OR=1.01; 99% CI: 0.98–1.05). The risk was also not increased in subgroup analyses by time since bereavement, risk of partner death, age, sex, and recent depression/anxiety

(a possible mediator). In contrast, study III showed that cases with zoster had a higher OR for previous mood disorder diagnosis compared with controls in both Denmark (1.15; 99% CI: 1.12–1.19) and the UK (1.12; 99% CI: 1.11–1.14). There was no substantial variation by time since last healthcare contact for the condition or severity defined based on codes for referral and treatment by specialists and hospitalization.

In **study IV**, we performed a systematic review and meta-analysis on zoster as a marker of occult cancer. Ten studies reported estimates for the risk of cancer among persons presenting with zoster. The pooled relative risk of cancer following zoster was 1.42 (95% CI: 1.18–1.71) overall and 1.83 (1.17–2.87) in the first year of follow-up. Considering studies reporting on individual types of cancer, the highest relative risk was observed for hematological cancers. The absolute risk of zoster in the first year was low (≤1.1% overall), and we found no studies on the benefits and harms of extensive examinations to facilitate earlier diagnosis of cancer at the time of zoster.

In conclusion, we have developed a valid algorithm for identifying patients with zoster in epidemiological studies using routinely collected prescription and hospital data. We have shown that zoster is a common disease among persons aged 50 years or older in Denmark, in particular among women, and its occurrence may be on the rise. In addition to severe immunosuppression, potential risk factors for zoster include various autoimmune conditions, chronic kidney disease, obstructive lung diseases, and inhaled glucocorticoids. Mood disorder may also increase risk, but the role of psychological stress is challenged by the lack of an association with partner bereavement. The finding that zoster may be triggered by occult cancer is intriguing, but clinical implications are limited by the low absolute cancer risk.

7. Dansk resumé (Danish summary)

Helvedesild er en smertefuld sygdom, som skyldes infektion med skoldkoppevirus, som har ligget latent i nervebanerne og bryder ud når det cellulære immunforsvar svækkes af den ene eller anden grund. Siden 2014 har det være muligt at blive vaccineret mod helvedesild i Danmark, men vaccinen er dyr og tilbydes ikke gratis. Selv om det er blevet anslået, at op til 50% af personer, som opnår en alder på 85 år, vil udvikle helvedesild, er vores viden om den samlede byrde af helvedesild i befolkningen og hvilke faktorer som øger risikoen for sygdommen begrænset. Verdenssundhedsorganisationen og Det Europæiske Center for Sygdomsforebyggelse og -kontrol har således understreget behovet for en bedre forståelse af forekomsten og fordelingen (=epidemiologien) af helvedesild i den almene befolkning. Desværre er sådanne data ikke tilgængelige i de fleste lande, herunder Danmark, fordi diagnoser af helvedesild ikke bliver registreret i almen praksis. Denne afhandling havde til formål at (i) udvikle en metode til at identificere helvedesild baseret på data fra apoteker og hospitaler som indsamles rutinemæssigt og (ii) udføre en række epidemiologiske undersøgelser om forekomsten af helvedesild og eventuelle risikofaktorer.

Studie I blev gennemført på data fra de danske sundhedsregistre. Først foretog vi et valideringsstudie i almen praksis for at undersøge, om en førstegangsrecept for systemisk aciclovir, valacyclovir og famciclovir kan bruges som et surrogatmål for helvedesild i primærsektoren. Ved en gennemgang af journalmateriale (n=86), var vi i stand til at bekræfte helvedesild blandt 87% personer, der havde indløst en recept der var forenelig med anbefalet behandling for helvedesild (800 mg acyclovir i pakker af 35 piller eller 500 mg tabletter af valacyclovir eller famciclovir). Vi brugte så denne definition, suppleret med diagnoser fra hospitalssektoren, til at studere forekomsten af helvedesild i Danmark i perioden 1997 til og med 2013. Vi identificerede 189.025 personer med helvedesild. Forekomsten af helvedesild steg fra 2,15 per 1000 person-år blandt 40-årige til 8,45 per 1000 person-år blandt 90-årige. Den aldersstandardiserede rate steg i løbet af studieperioden. Forekomsten var hyppigere hos kvinder end hos mænd. Ca. 3,5% af personer var blevet diagnosticeret med helvedesild under en hospitalsindlæggelse. Ved sammenligning med populationskontroller af samme alder og køn (n=945.111, fandt vi en forøget risiko for helvedesild blandt personer med leddegigt (27% stigning), subakut/systemisk lupus erythematosus (64%), inflammatorisk tarmsygdom (29%), kronisk obstruktiv lungesygdom (20%), astma (19%), kronisk nyresygdom (51%), type I sukkersyge (13%), og brugere af inhalationssteroid (18%). Som forventet var det en særlig stor procentmæssig stigning i risiko for helvedesild blandt personer med svær immunsvækkelse, herunder humant immundefektvirus (272% stigning), leukæmi (157%), lymfom (273%), myelom (312%), knoglemarvs-/stamcelle-transplantation (96%), anden cellulær immundefekt (70%), og behandling med binyrebarkhormon (70%) eller andre immunsupprimerende lægemidler (82%). Samlet var 8,2% af helvedesildspatienterne svært immunsvækkede.

I studie II og III undersøgte vi om psykisk stress kan udløse helvedesild. I **studie II**, brugte vi dødsfald af en partner som et surrogatmål for ekstrem stress. I studie III, undersøgte vi sammenhængen med diverse affektive og stress-relaterede sindslidelser, herunder depression, angst, og reaktioner på svær belastning og

tilpasningsreaktioner (f.eks. posttraumatisk stress), da disse tilstande typisk er forbundet med kronisk stress. Vi gennemførte studierne i både Danmark (1997–2013) og Storbritannien (2000–2013). Vi inkluderede over 150.000 personer med helvedesild i hvert land og op til 4 gange så mange kontrolpersoner. Vi fandt ingen sammenhæng mellem partnerens død og helvedesild i Danmark. Risikoen var heller ikke forøget i analyser hvor vi tog højde for tid siden dødsfaldet, hvorvidt partneren havde en høj forventet risiko for at dø, alder, køn eller nylig depression/angst. I modsætning viste dog både de danske og britiske data i **studie III** at personer med de nævnte sindslidelser havde en 12%–15% højere risiko for helvedesild sammenlignet med personer uden disse lidelser. Denne sammenhæng var uafhængig af tiden siden sidste lægekontakt for tilstanden eller sværhedsgrad (defineret ud fra koder for henvisning/behandling af speciallæge eller hospitalsindlæggelse).

I **studie IV** foretog vi en systematisk gennemgang af de studier, som har undersøgt hvorvidt helvedesild er en markør for en underliggende, ikke-diagnosticeret kræftsygdom. Baseret på ti studier var den samlede risiko for kræft øget med 42% blandt personer med helvedesild, og dette tal steg til 83% når det første år efter helvedesild blev undersøgt selvstændigt. I undersøgelser, der rapporterede om de enkelte former for kræft, fandt vi en særlig høj procentmæssig stigning i risikoen for blod, lymfe, og knoglemarvskræft. Den absolutte risiko for helvedesild i det første år var dog samlet set lav (≤1.1%). Der eksisterer ingen undersøgelser af fordele og ulemper ved at lave omfattende undersøgelser for kræft hos patienter som bliver diagnosticeret med helvedesild.

I det foreliggende arbejde har vi udviklet en valid metode til at identificere patienter med helvedesild i epidemiologiske studier baseret på rutinemæssigt indsamlede data fra apoteker og hospitaler. Vi fandt, at helvedesild var en almindelig sygdom blandt personer i alderen 50 år eller ældre i Danmark, især kvinder, og at forekomsten muligvis er stigende. Udover svær immunsvækkelse, var autoimmune tilstande, kronisk nyresygdom, obstruktiv lungesygdom og brug af inhalationssteroider forbundne med en øget risiko for helvedesild. Forekomsten var også forhøjet blandt personer med sindslidelser, såsom angst og depression. Det er dog uklart om psykisk stress kan forklare denne sammenhæng, da personer som for nyligt havde mistet en partner, hvilket er en meget stressende livsbegivenhed, ikke havde en øget risiko. Endelig fandt vi, at helvedesild muligvis kan udløses af underliggende kræft, men de klinik konsekvenser heraf er begrænsede da den absolutte risiko for kræft trods alt var lav.

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9. Appendices

Appendices I–V provide the full versions of papers I–IV:

- **Appendix I**:

Paper I

- **Appendix II**:

Paper II

- **Appendix III**:

Paper III

- **Appendix IV**:

Paper IV

Title: Prevaccination epidemiology of herpes zoster in Denmark: quantification of occurrence and risk factors

Running title: Epidemiology of herpes zoster in Denmark

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Highlights

- An algorithm to identify zoster in the Danish health registries was examined
- Zoster was identified using routinely collected prescription and hospital records
- Zoster was confirmed in 87% who dispensed an antiviral recommended for zoster
- Rates increased from 2.15 to 9.45 per 1000 person-years between age 40 and 90 years
- Rates were higher in persons with immunosuppression and certain chronic diseases

ABSTRACT

Background: Herpes zoster (HZ) is a vaccine-preventable disease caused by reactivation of the varicella-zoster virus. Unfortunately, formulation of recommendations on routine immunization is hampered by a lack of data on disease burden, since most countries do not record cases of HZ in the general population. We developed and validated an algorithm to identify HZ based on routinely collected prescription and hospital data and used it to quantify HZ occurrence and risk factors in Denmark prior to marketing of the HZ vaccine.

Methods: We included patients aged ≥40 years with a first-time systemic Acyclovir, Valacyclovir, or Famciclovir prescription or a hospital-based HZ diagnosis in the Danish nationwide health registries during 1997–2013. First, we validated the proportion of persons with HZ among those with antiviral prescriptions. Second, we computed age-specific rates of HZ. Third, we computed odds ratios (ORs) for common chronic diseases and immunosuppressive factors among HZ cases *vs.* matched population controls.

Results: Medical record review confirmed HZ in 87% (95% confidence interval: 79%–93%) of persons ≥40 years who dispensed antivirals at doses recommended for HZ. HZ rates increased from 2.15/1000 person-years in 40-year-olds to 9.45/1000 person-years in 95-year-olds. Rates were higher in women than in men. Approximately 3.5% of persons had zoster diagnosed during hospitalization. As expected, persons with severe immunosuppressive conditions had the highest ORs of HZ (between 1.82 and 4.12), but various autoimmune diseases, asthma, chronic kidney disease, and use of inhaled glucocorticoids were also associated with increased ORs (between 1.06 and 1.64).

Conclusion: This algorithm is a valid tool for identifying HZ based on routine healthcare data. It shows that HZ is common in Denmark, especially in patients with certain chronic conditions.

Prioritized vaccination of such high-risk patients might be an option in countries considering alternatives to universal vaccination.

Keywords: epidemiology; health administrative data; herpes zoster; incidence; risk factors; validation

Introduction

Herpes zoster (HZ) is characterized by a painful vesicular rash caused by reactivation of the varicella zoster virus (VZV), which is acquired as chickenpox in childhood [1]. Reactivation is triggered by decreased immune function, such as that observed with increasing age or due to immunosuppressive diseases or treatments [1]. A common complication of HZ is post-herpetic neuralgia, a pain syndrome, which is often associated with poor response to analgesics and decreased quality of life [2].

In 2006, the European Medicines Agency authorized marketing of a live-attenuated VZV vaccine (Zostavax®) to reduce the incidence of HZ and post-herpetic neuralgia in adults aged ≥50 years [1]. The World Health Organization and the European Centre for Disease Prevention and Control offer no recommendations on routine immunization due to uncertainties regarding persistence of immunity, optimal vaccination schedules, and lack of data on the HZ burden in most countries [1]. The high vaccine price further adds doubts to cost-effectiveness [1]. Vaccination of highly susceptible individuals may provide an alternative to routine immunization, but such vaccine policies require quantification of HZ risk factors in the population.

The European Centre for Disease Prevention and Control has also stressed the need for better understanding of the epidemiology of HZ [3]. Unfortunately, most European countries have no national mandatory or sentinel surveillance of HZ in primary care where most cases are diagnosed [3]. In Denmark, for example, most studies have thus been limited to hospital-based clinics, which presumably represent persons with severe infections or comorbid disease [4].

We developed and validated an algorithm to identify HZ based on prescription and hospital records in the Danish nationwide health registries and used it to quantify age-specific rates and risk factors for HZ during the 17-year period prior to marketing of Zostavax.

Methods

The Danish healthcare system guarantees tax-financed healthcare for all residents [5]. General practitioners (GPs) represent the cornerstone of the primary sector as gatekeepers, providing referral to specialists when needed. Although copayment of prescription drugs is required, a drug reimbursement program limits yearly out-of-pocket expenditures [6]. Residents' healthcare utilization is recorded in various registries using unique civil personal registration (CPR) numbers, which are assigned by the Civil Registration System [5].

In Denmark, recommended first-line treatment for HZ is a seven-day course of 800 mg Acyclovir five times daily or 500 mg Valacyclovir or Famciclovir three times daily [7]. These antiviral nucleoside analogues are also approved for chickenpox, herpes simplex, and cytomegalovirus infections [7]. No national vaccination programs against chickenpox or HZ have yet been implemented in Denmark. Zostavax was marketed in September 2014, but its cost is not reimbursed by the public healthcare system.

Algorithm for identifying herpes zoster

As a proxy for HZ treated in primary care, we identified all persons with a prescription for systemic Acyclovir, Valacyclovir, or Famciclovir in the Danish National Prescription Registry during January 1, 1997–December 31, 2013. Prescription drugs dispensed at all Danish pharmacies since January 1, 1995 are recorded in this Registry, including the dispensing date, the number of packages and Nordic article number of the drug (which encodes strength, package size, and Anatomical Therapeutic Chemical code), and unique patient, prescriber, and pharmacy identifiers [6]. We required that persons be aged ≥40 years at time of prescription redemption and have no previous prescription record for any of the three antiviral drugs. We applied these eligibility criteria to avoid misclassification of treatment for severe primary or reactivating herpes simplex infections,

which are primarily seen among young adults [8] and can require longer-term suppressive or episodic therapy [7]. The age restriction also limited inclusion of patients treated for chickenpox [1]. In addition to a 'broad definition' including antivirals of any dose, we developed a 'HZ-specific definition' restricted to prescriptions for tablet doses and package sizes most compatible with treatment for HZ (800 mg Acyclovir in packets with 35 pills or 500 mg Valacyclovir/Famciclovir).

We used the Danish National Patient Registry to identify all hospital-based inpatient, outpatient specialty clinic, and emergency room contacts, with HZ as primary or secondary diagnosis, among persons aged ≥40 years. This nationwide hospital registry contains data on all inpatient, outpatient specialty clinic, and emergency room contacts since 1995, and non-psychiatric admissions during 1977–1994 [9]. A primary diagnosis (the main reason for contact) and secondary diagnoses are recorded at time of discharge or end of outpatient contact according to *the International Classification of Diseases, Eighth Revision* until the end of 1993 and *Tenth Revision* thereafter [9]. Hospital examinations and specialized treatments (*e.g.*, chemotherapy) are recorded at delivery.

We considered the date of first-time HZ diagnosis or dispensing of an antiviral prescription to be the index date for HZ, whichever came first if both were present. Persons with a diagnosis and prescription on the same day were assigned to the HZ diagnosis group. In analyses of hospital-based HZ diagnoses, we included all persons with a diagnosis (regardless of previous antiviral prescriptions), in order to capture also patients who required hospital referral following a GP contact. Definitions for HZ and other variables are presented in Supplementary Methods 1.

Validation

We examined the validity of antiviral medications as proxies for HZ among 10 GPs in the Central Denmark Region. We selected GPs among practices who were active at the time of study

(September 2016) and willing to provide data for research. For each general practice, we randomly sampled up to 20 patients aged ≥40 years who had dispensed a first-time prescription for Acyclovir, Valacyclovir, or Famciclovir issued by the GP during January 1, 2007–December 31, 2012. The validation sample derived from the Health information system for the Central Denmark Region, which includes patient-identifiable data from the Aarhus University Prescription Database [6]. We sent GPs an invitation letter describing the aim, content, and honorarium for participation (129.32 Danish kroner per 10 minutes of time, according to the General Practice agreement). Consenting GP practices (90%) received a questionnaire with a checklist of indications for treatment (HZ, herpes simplex, other, or unknown) for each patient. To facilitate look-up in the medical records, the questionnaire provided patients' CPR number, type of prescription (drug, dose, and number of pills), and the date of dispensing. We collected data during October 1, 2016–January 4, 2017. We sent two reminders to GPs who did not respond to the initial invitation.

Herpes zoster risk factors

To quantify risk factors for HZ, we designed a case-control study. For each case with HZ identified by our algorithm, we used the Civil Registration System to identify up to five population controls who were alive and living in Denmark on the diagnosis date and had the same sex and birth year (*i.e.*, risk-set sampling [10]). We excluded controls with previous HZ. Controls were assigned an index date identical to their case. We then used data from the Danish National Prescription Registry and/or the Danish National Patient Registry to identify records indicating presence of rheumatoid arthritis, systemic/subacute lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes (type I, type II, or unknown), chronic kidney disease, human immunodeficiency virus (HIV) infection, hematopoietic stem cell transplantation, or another cellular immune deficiency at any time before the index date; leukemia, lymphoma, or myeloma

within two years before the index date; depression within one year before index date; and treatment with oral glucocorticoids, other immunosuppressant drugs, or inhaled glucocorticoids within 90 days before the index date (Supplementary Methods 1). Severe immunosuppression, including HIV, leukemia, lymphoma, myeloma, hematopoietic stem cell transplantation, other cellular immune deficiency, oral glucocorticoids, and other immunosuppressants, was considered contraindication for use of Zostavax [1].

Statistical analysis

In the validation study, we computed the positive predictive value (PPV) as the proportion of patients with a first-time antiviral prescription who had HZ as an indication for treatment. We used Wilson´s score method to compute 95% confidence intervals (CIs). We stratified results by calendar period, age group, and sex.

In the nationwide data, we computed the age-specific rate of HZ using population denominators recorded by the Civil Registration System on January 1st of each year. To further validate our algorithm, we plotted the results together with age-specific rates reported for other European countries, identified by a systematic literature search (Supplementary Methods 2). Next, we used conditional logistic regression to compute odds ratios (ORs) with 99% CIs for each risk factor among HZ cases *vs.* controls. Because of the risk-set sampling of controls, the ORs provide unbiased estimates of the incidence rate ratio [10]. We compared three regression models for each risk factor: Model 1 included no other variables; Model 2 included all other potential risk factors except inhaled glucocorticoids, oral glucocorticoids, and other immunosuppressants; and Model 3 contained all variables. We specifically ascertained the number of HZ patients aged ≥50 years without a contraindication, *i.e.*, those originating from the target population for Zostavax. We performed analyses for prescription-based and diagnosis-based cases combined and individually.

Results

Validation study

Nine out of 10 invited practices agreed to participate in the validation study. The age and sex distribution considering all users of prescriptions issued by participating practices (median age 61 years [interquartile range: 51–70 years]; 65.5% women) was similar to that observed in remaining practices in the region (median age 61 years [interquartile range: 50–72 years]; 63.3% women).

Among participating GPs, we sampled a total of 176 first-time users of an antiviral medication. However, we could not identify medical records for 34 patients who had never been registered with the issuing practice. These prescriptions were most likely issued to a patient from another practice during GPs' out-of-hours services. The PPVs, *i.e.*, the proportions of patients with HZ as indication for treatment, for the remaining 142 patients were 58% (95% CI: 50%–66%) for any antiviral prescription and 87% (95% CI: 79%–93%) for the HZ-specific prescriptions. The HZ-specific definition had a sensitivity of 90% (95% CI: 82–95%) compared with the broad definition. We observed no substantial variation by calendar period, but the PPV was lower among women and in the youngest age groups (Table 1).

Based on the low validity for any antiviral prescription, our final algorithm was based on antiviral mediciations at HZ-specific doses supplemented with hospital-based diagnoses.

Rate

Characteristics for the 189,025 persons identified by our algorithm are provided in Table S1. Hospitalization occurred in 6,560 persons (3.5%). Acyclovir was the most frequent antiviral agent defining HZ (84.7%), followed by Valacyclovir (14.0%) and Famciclovir (1.3%). Among persons aged ≥50 years, 146,067 (91.8%) had no contraindication against Zostavax (*i.e.*, were not

considered severely immunosuppressed).

The crude HZ rate was 4.17 per 1000 person-years, increasing consistently from 2.15 (95% CI: 2.07–2.23) per 1000 person-years at age 40 years to 9.45 (95% CI: 8.89–10.01) per 1000 person-years at age ≥95 years (Figure 1); the increase in age-dependent HZ rates was particularly strong for hospital-based diagnoses (Figure 2). The rate was higher for women than men at all ages (Figure S1).

The age-specific HZ rate estimated by our algorithm is consistent with (although in the lower range of) rates reported by previous European studies (Figure 3) [11-20]. The hospitalization rate is in the mid-range of the rates reported in other countries (Figure S2) [14,16,21-28].

Risk factors

The case-control study yielded the highest ORs for factors associated with severe immunosuppression (Table 2). The ORs attenuated with each model but remained elevated for all exposures in Model 3 (from 1.06 for type II diabetes to 4.12 for myeloma). Multimorbidity and use of inhaled glucocorticoids, oral glucocorticoids, and other immunosuppressants thus partly explained the associations. With the exception of inhaled corticosteroids, ORs were higher for persons with hospital-based diagnoses of HZ than for those defined by HZ-specific prescriptions (Table S2). The median age and proportion of men were also higher (Table S1).

Discussion

We used routinely-collected data on dispensed prescriptions and hospital diagnoses from the Danish nationwide health registries to develop an algorithm that identifies HZ for population-based epidemiological studies. Among those identified by a HZ-specific antiviral prescription, 87% had a compatible diagnosis in the medical record. Consistent with previous studies, the estimated rate of

HZ increased with age and was highest in women and persons with diseases and treatments associated with immune dysregulation. Other chronic conditions (*e.g.*, chronic obstructive pulmonary disease and asthma) and use of inhaled glucocorticoids were also associated with increased risks.

Studies on HZ in Danish general practice are sparse [29,30]. Among 276 general practices volunteering in a study from 1985, the incidence of HZ increased from one per 1000 person-years in those aged <10 years to 5.5 per 1000 person-years among those aged 90 years [29]. These estimates are considerably lower than ours, which may be explained by an increasing incidence, underreporting from participating practices, or exclusion of immune incompetent patients (unclear if these were also excluded from denominators). In a more recent study from 2009, the overall incidence proportion of self-reported HZ was 13.8% among 1207 individuals aged >50 years [30]. Comparison with this study is also limited, because of the different design, potential recall bias, and selection bias, as participants were recruited through influenza vaccination campaigns.

The strengths of our study rest on the comprehensive coverage of the data sources. The Danish National Prescription Registry collects data from all community pharmacies in Denmark, including prescriptions issued by private specialists (*e.g.*, dermatologists) and drugs used by nursing home residents, limiting misclassification due to frailty [6]. Inclusion of diagnoses from outpatient specialty clinic visits in the Danish National Patient Registry is also an important advantage, as HZ in persons with chronic diseases (*e.g.*, cancer) may be diagnosed during ambulatory care. Finally, the Civil Registration System provided the possibility to obtain accurate population denominators and individual-level data, enabling us to estimate numbers of persons with first-time HZ rather than aggregate number of contacts for HZ.

Limitations of our validation study warrant discussion. We included research-interested GPs in one of five Danish regions. Furthermore, one practice declined participation. Nevertheless, we

have no reason to believe that the indication for prescribing antiviral medications for HZ is different among non-participating practices, given similar demographics of treated patients. Another concern is that we could not obtain medical records concerning the indication for prescription for 19% who were not registered with the issuing practice. However, the proportion of HZ-specific prescriptions was very similar for missing and non-missing records (59% *vs.* 61%).

We used data on tablet count and strength to increase the specificity of acyclovir prescriptions towards zoster. However, as it is more difficult to differentiate between indications for Valacyclovir and Famciclovir based on tablet count and strength, we chose a more inclusive definition for these drugs. As Acyclovir predominated in our patient population, we cannot rule out that the validity is lower for Valacyclovir and Famciclovir. Finally, although a record of HZ in the medical record is not a perfect gold standard, one study found a PPV of 95% for GP-diagnosed HZ compared with Polymerase Chain Reaction [31].

Presumably our final algorithm did not capture primary care patients who were not treated with antivirals, patients who received an antiviral medication at a non-HZ-specific dose (estimated 10%), and patients who did not seek care for HZ. In accordance with treatment recommendations [7], we expect that incompleteness is greatest for persons in their 40s and persons presenting for care ≥72 hours after rash onset. It is likely that such false negatives outnumber the 13% false positive rate estimated in our validation study. Although we found large variation in age-specific rates across Europe, comparison with the neighboring country Sweden suggests roughly 80% sensitivity. The proportion of HZ patients treated with antiviral medication varies largely across countries (50% to >95%), limiting reliable extension to our data for the purpose of estimating completeness. The higher rate in women is consistent with that observed in other European countries [11,13,15-18].

The validity of our algorithm is also shown through comparison with previous population-

based studies on HZ risk factors [12]. Using similar design and exposure definitions, we were able to replicate the findings from the most comprehensive previous risk factor study conducted in the United Kingdom (UK) primary care [12]. A comparison of the fully adjusted ORs is provided in Figure 4. Our estimates were higher for chronic kidney disease, leukemia, myeloma, and oral glucocorticoids, and lower for HIV and hematopoietic stem cell transplantation. These differences may be explained by more complete identification of severe conditions in our study, partly because the UK study used only GP records to identify exposures. Indeed, estimates reported in a recent UK study, that included also inpatient hospital data for 60% of patients, where even closer to ours [32]. Increased, albeit highly variable, relative risk estimates are also reported in previous studies on rheumatoid arthritis [33,34], systemic lupus erythematosus [33,34], inflammatory bowel disease [34-37], asthma [38-42], chronic obstructive pulmonary disease [38,43,44], chronic kidney disease [45], and/or severe immunosuppressive factors [38-40]. For diabetes [38-40,44,46-48], depression [39,40,44], and inhaled glucocorticoids [49], findings are more controversial. This variation may be explained by differences in study designs, exposure definitions (*e.g.*, severity of kidney disease [45]), risk of selection bias and residual confounding, and participants' healthcare access and ethnicity. For example, few previous studies on diabetes distinguished between type I and type II diabetes [12,39,47,48].

Immunosuppression induced by disease processes or treatments may both explain the associations observed in our study. We thus cannot rule out that severity of disease explains entirely the increased OR for inhaled glucocorticoids. Conversely, incomplete data on hospital-based immunosuppressive treatments may have caused residual counfounding of the fully adjusted ORs for autoimmune diseases. Finally, increased medical attention leading to detection of HZ may also explain the relatively modest associations observed for *e.g.* type II diabetes.

Most European countries have not implemented routine vaccination with Zostavax, partly due

to high costs. Furthermore, the strongest risk factor (severe immunosuppression) contraindicates vaccination due to risk of viral replication. A new subunit vaccine is being tested in immune competent and incompetent adults, showing safety and 90% efficacy for preventing HZ ≥4 years post-vaccination [50]. While awaiting further data, our results add to previous evidence by identifying high-risk groups, which could be targeted for vaccination.

ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

None.

ETHICS

The project was approved by the Danish Data Protection Agency (record number: 1-16-02-370-14). For the validation substudy, access to non-anonymized data and information from medical records were approved separately by the Danish Data Protection Agency (record number: 1-16-02-120-15), the Danish Health and Medicines Authorities (record number: 3-3013-1084/1), the Committee of Multipractice Studies in General Practice (record number: MPU 12-2015), and the Health information system for the Central Denmark Region.

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Table and Figure legends

Table 1

Positive predictive value of antiviral prescriptions as a proxy for herpes zoster.

Table 2

Risk factors for herpes zoster among 189,025 cases and 945,111 matched controls, Denmark, 1997–2013.

Figure 1

Age-specific rate of herpes zoster with 95% confidence intervals according to the overall algorithm, Denmark, 1997–2013.

Figure 2

Age-specific rates of hospital-based herpes zoster diagnoses, overall and by type of diagnosis, Denmark, 1997–2013.

Figure 3

Age-specific rates of herpes zoster in the present study compared with those reported by previous European studies.

Figure 4

Adjusted odds ratios with 99% confidence intervals for potential risk factors for herpes zoster in the present study and a previous study from the United Kingdom.*

Abbreviations: CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; HSCT=hematopoietic stem cell transplantation; IBD=inflammatory bowel disease; OID=other immunosuppressive disease; SLE=subacute/systemic lupus erythematosus

*Forbes *et al*. Quantification of risk factors for herpes zoster: population based case-control study. BMJ. 2014; 348:g2911

Table 1

Positive predictive value of antiviral prescriptions as a proxy for herpes zoster.

	Any prescription				HZ-specific prescriptions			
	Sample	Confirmed	Missing	PPV, % (95% CI)	Sample	Confirmed	Missing	PPV, % (95% CI)
Overall	176	83	34	58 (50–66)	106	75	20	87 (79–93)
Sex								
Women	112	48	21	53 (43–63)	65	44	12	83 (71–91)
Men	64	35	13	69 (55–80)	41	31	8	94 (80–98)
Age group (years)								
40–49	41	6	12	21 (10–38)	9	5	1	62 (31–86)
50–59	53	19	10	44 (30–59)	29	15	9	75 (53–89)
60–69	48	32	6	76 (61–87)	40	31	6	91 (77–97)
70–79	24	20	2	91 (72–97)	19	18	1	100 (82–100)
80+	10	6	4	100 (61–100)	9	6	3	100 (61–100)
Year of prescription								
2007–2009	66	30	13	57 (43–69)	38	25	9	86 (69–95)
2010–2012	110	53	21	60 (49–69)	68	50	11	88 (77–94)

Abbreviations: CI=confidence interval; HZ=herpes zoster; PPV=positive predictive value

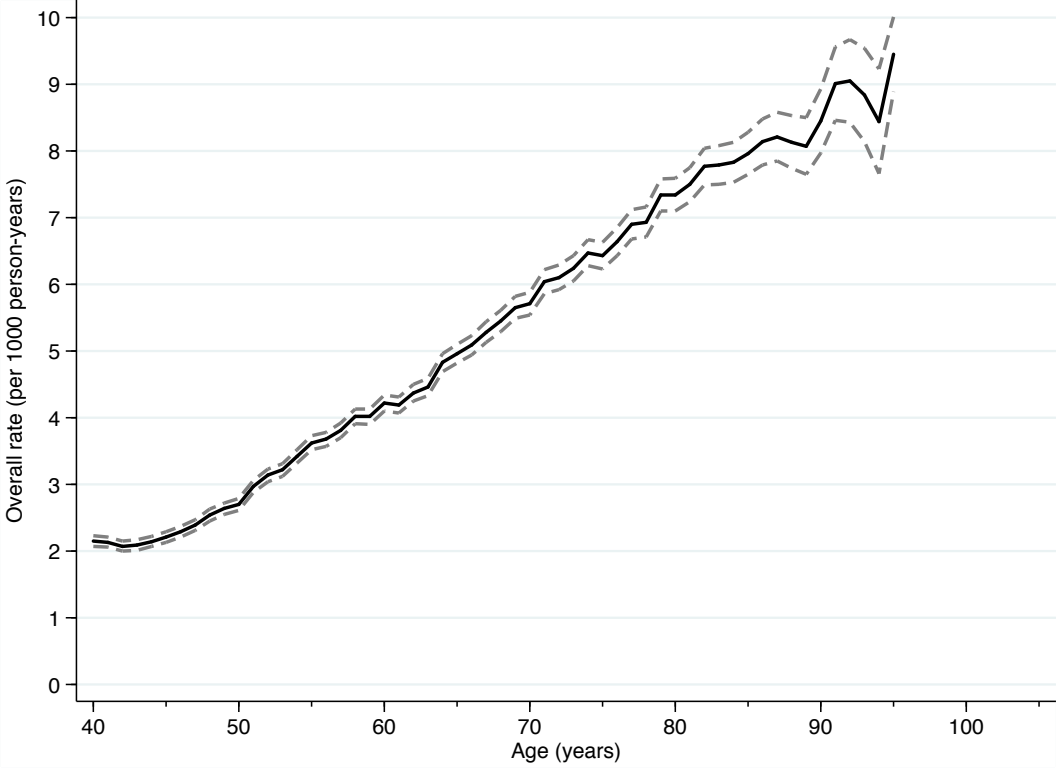
Table 2

Risk factors for herpes zoster among 189,025 cases and 945,111 matched controls, Denmark, 1997–2013.

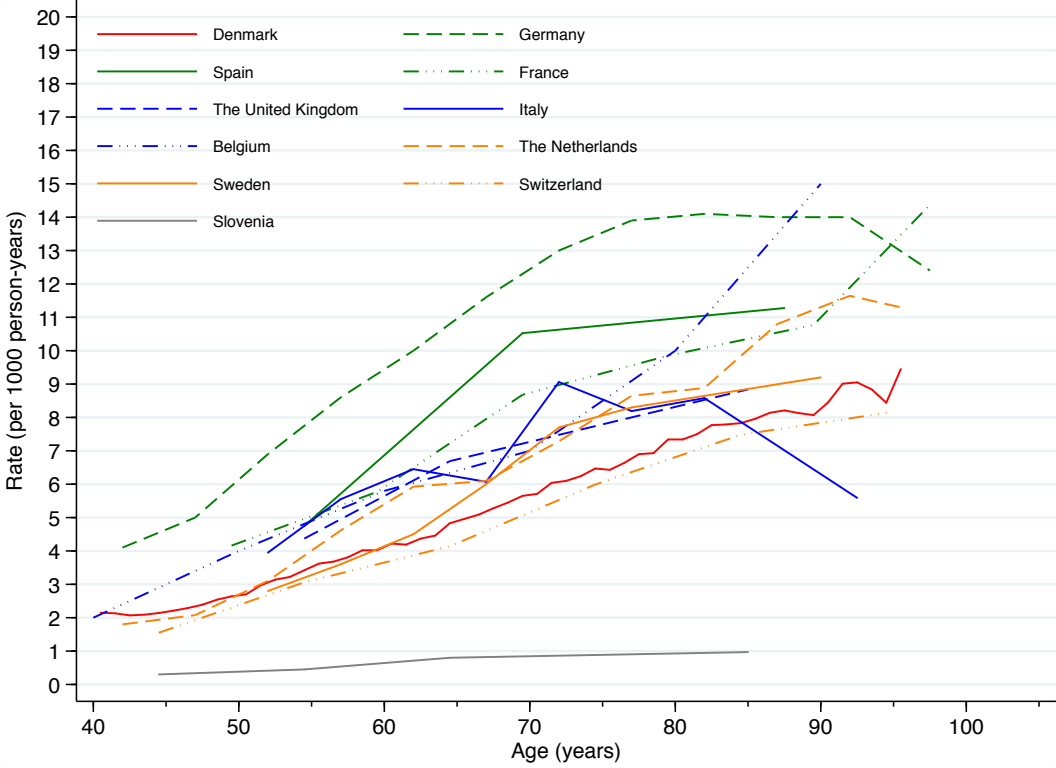
	Cases, n (%)	Controls, n (%)	Odds ratios (99% CI)*		
			Model 1	Model 2	Model 3
Rheumatoid arthritis	4172 (2.21)	12,146 (1.29)	1.74 (1.66–1.82)	1.67 (1.59–1.75)	1.27 (1.21–1.34)
SLE	469 (0.25)	1032 (0.11)	2.28 (1.97–2.63)	1.98 (1.71–2.29)	1.64 (1.41–1.90)
IBD	2672 (1.41)	9389 (0.99)	1.43 (1.35–1.51)	1.37 (1.30–1.46)	1.29 (1.22–1.37)
COPD	11,392 (6.03)	40,039 (4.24)	1.46 (1.42–1.51)	1.40 (1.36–1.45)	1.20 (1.16–1.24)
Asthma	2740 (1.45)	10,060 (1.06)	1.37 (1.29–1.45)	1.37 (1.30–1.45)	1.19 (1.12–1.26)
CKD	2970 (1.57)	7795 (0.82)	1.93 (1.83–2.04)	1.59 (1.50–1.69)	1.51 (1.43–1.61)
Depression	25,390 (13.43)	106,846 (11.31)	1.22 (1.20–1.25)	1.18 (1.16–1.21)	1.17 (1.15–1.19)
Diabetes	14,057 (7.44)	64,053 (6.78)	1.11 (1.08–1.14)	1.06 (1.04–1.09)	1.06 (1.04–1.09)
Type I	358 (0.19)	1497 (0.16)	1.20 (1.03–1.40)	1.14 (0.98–1.33)	1.13 (0.97–1.32)
Type II	12,431 (6.58)	57,173 (6.05)	1.10 (1.07–1.13)	1.06 (1.03–1.09)	1.06 (1.03–1.08)
Unknown	1268 (0.67)	5383 (0.57)	1.19 (1.09–1.29)	1.13 (1.04–1.22)	1.12 (1.03–1.21)
Inhaled glucocorticoids	11,374 (6.02)	40,742 (4.31)	1.43 (1.39–1.47)	–	1.18 (1.14–1.22)
HIV	345 (0.18)	449 (0.05)	3.86 (3.21–4.64)	3.72 (3.09–4.49)	3.72 (3.08–4.48)
Leukemia	856 (0.45)	1103 (0.12)	3.90 (3.47–4.39)	2.75 (2.42–3.13)	2.57 (2.26–2.93)
Lymphoma	1344 (0.71)	1302 (0.14)	5.19 (4.70–5.74)	4.22 (3.80–4.68)	3.73 (3.36–4.15)
Myeloma	542 (0.29)	354 (0.04)	7.66 (6.42–9.13)	5.08 (4.21–6.13)	4.12 (3.41–4.99)
HSCT	738 (0.39)	627 (0.07)	5.89 (5.12–6.77)	1.99 (1.69–2.34)	1.96 (1.66–2.31)
OID	294 (0.16)	461 (0.05)	3.20 (2.64–3.88)	1.76 (1.43–2.17)	1.70 (1.38–2.10)
Oral glucocorticoids	8862 (4.69)	19,702 (2.08)	2.33 (2.26–2.42)	–	1.87 (1.81–1.94)
Other immunosuppressants	4435 (2.35)	8247 (0.87)	2.74 (2.61–2.88)	–	1.82 (1.73–1.92)

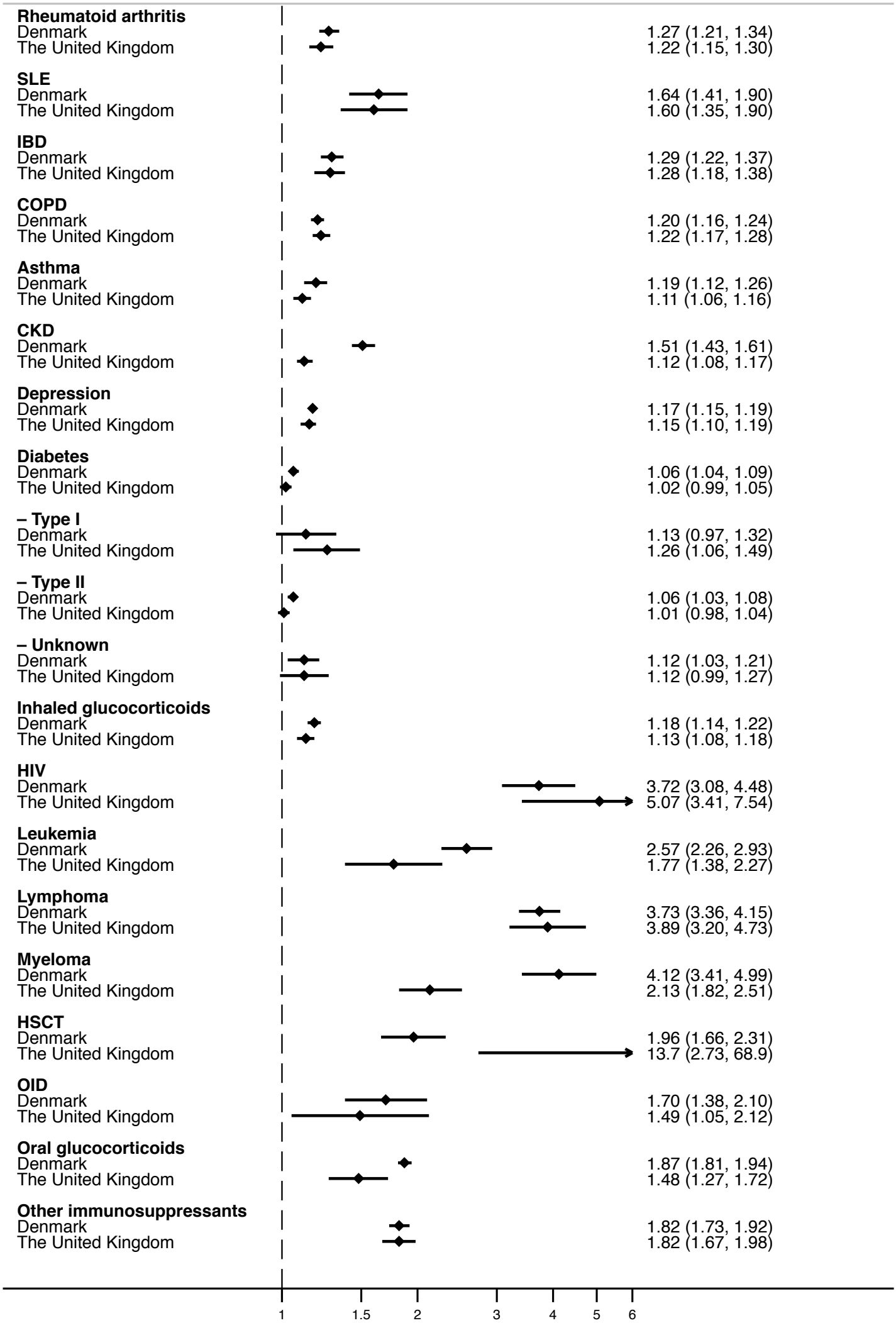
Abbreviations: CI=confidence interval; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; HSCT=hematopoietic stem cell transplantation; IBD=inflammatory bowel disease; OID=other cellular immune deficiency; SLE=subacute/systemic lupus erythematosus

*Computed using conditional logistic regression. Model 1 included no other variables. Model 2 included rheumatoid arthritis, SLE, IBD, COPD, asthma, CKD, depression, diabetes (any type), HIV, leukemia, lymphoma, myeloma, HSCT, and OID. Model 3 included inhaled glucocorticoids, oral glucocorticoids, and other immunosuppressants in addition to all variables in model 2. When examining types of diabetes, separate models were run for each type instead


Overall rate (per 1000 person-years)
0
1
2
3
4
5
6
7
8
9
10
40
50
60
70
80
90
100
Age (years)


All hospital-based diagnoses
All inpatient diagnoses
Inpatient primary diagnoses
Outpatient specialty clinic diagnoses
Emergency room diagnoses
Hospital diagnosis rate (per 1000 person-years)
0
.1
.2
.3
.4
.5
.6
.7
.8
.9
1
1.1
40
50
60
70
80
90
100
Age (years)


Denmark
Germany
Spain
France
The United Kingdom
Italy
Belgium
The Netherlands
Sweden
Switzerland
Slovenia
Rate (per 1000 person-years)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
40
50
60
70
80
90
100
Age (years)


Rheumatoid arthritis
Denmark 1.27 (1.21, 1.34)
The United Kingdom 1.22 (1.15, 1.30)
SLE
Denmark 1.64 (1.41, 1.90)
The United Kingdom 1.60 (1.35, 1.90)
IBD
Denmark 1.29 (1.22, 1.37)
The United Kingdom 1.28 (1.18, 1.38)
COPD
Denmark 1.20 (1.16, 1.24)
The United Kingdom 1.22 (1.17, 1.28)
Asthma
Denmark 1.19 (1.12, 1.26)
The United Kingdom 1.11 (1.06, 1.16)
CKD
Denmark 1.51 (1.43, 1.61)
The United Kingdom 1.12 (1.08, 1.17)
Depression
Denmark 1.17 (1.15, 1.19)
The United Kingdom 1.15 (1.10, 1.19)
Diabetes
Denmark 1.06 (1.04, 1.09)
The United Kingdom 1.02 (0.99, 1.05)
– Type I
Denmark 1.13 (0.97, 1.32)
The United Kingdom 1.26 (1.06, 1.49)
– Type II
Denmark 1.06 (1.03, 1.08)
The United Kingdom 1.01 (0.98, 1.04)
– Unknown
Denmark 1.12 (1.03, 1.21)
The United Kingdom 1.12 (0.99, 1.27)
Inhaled glucocorticoids
Denmark 1.18 (1.14, 1.22)
The United Kingdom 1.13 (1.08, 1.18)
HIV
Denmark 3.72 (3.08, 4.48)
The United Kingdom 5.07 (3.41, 7.54)
Leukemia
Denmark 2.57 (2.26, 2.93)
The United Kingdom 1.77 (1.38, 2.27)
Lymphoma
Denmark 3.73 (3.36, 4.15)
The United Kingdom 3.89 (3.20, 4.73)
Myeloma
Denmark 4.12 (3.41, 4.99)
The United Kingdom 2.13 (1.82, 2.51)
HSCT
Denmark 1.96 (1.66, 2.31)
The United Kingdom 13.7 (2.73, 68.9)
OID
Denmark 1.70 (1.38, 2.10)
The United Kingdom 1.49 (1.05, 2.12)
Oral glucocorticoids
Denmark 1.87 (1.81, 1.94)
The United Kingdom 1.48 (1.27, 1.72)
Other immunosuppressants
Denmark 1.82 (1.73, 1.92)
The United Kingdom 1.82 (1.67, 1.98)
1
1.5
2
3
4
5
6

Supplementary Methods 1. Definition of study variables

The registry codes used to identify herpes zoster (HZ) and potential risk factors are shown in the Table below. We specifically aimed to examine whether previously established risk factors for HZ could be reproduced with our algorithm. We thus designed a nested case-control study similar to a previous general practice-based study from the United Kingdom [1], a country with a healthcare system comparable to Denmark's. The UK study is the largest risk factor study published to date and was based on data recorded in the Clinical Practice Research Datalink, which collects data from almost 700 general practices in the UK.

In the present study, we used the Danish National Prescription Registry and the Danish National Patient Registry to retrieve information on presence of the following variables among HZ cases and controls: rheumatoid arthritis, systemic/subacute lupus erythematosus (SLE), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), asthma, diabetes (type I, type II, or unknown type), chronic kidney disease (CKD), human immunodeficiency virus (HIV) infection, hematopoietic stem cell transplantation (HSCT), or other cellular immune deficiency (OID) at any time before the index date; leukemia, lymphoma or myeloma within two years before the index date; depression within one year before the index date; and prescription records for oral glucocorticoids, other immunosuppressant drugs, or inhaled glucocorticoids within 90 days before the index date. For COPD, we considered incident diagnoses of chronic bronchitis and/or emphysema at age 35 years or older. For asthma, we required that patients (1) had a previous asthma diagnosis, (2) had redeemed an asthma-related prescription within the year before the index date, and (3) were not classified as having COPD. Diabetes was identified as any previous diabetes diagnosis or two or more antidiabetic prescriptions. Women identified solely by monotherapy with metformin at ages 20–39 years were not considered, because they may have had polycystic ovarian syndrome as the indication for their prescription. We classified type I diabetes as (1) age at first diagnosis ≤35 years and exclusive treatment with insulin prior to index date or (2) ≥2 insulin prescriptions at ages ≤35 years, but no diabetes diagnosis. Type II diabetes was defined as (1) age at first diabetes diagnosis >35 years or (2) exclusive treatment with oral anti-diabetics at ages >35 years. Remaining diabetes patients were considered to have unknown type. CKD included codes for chronic kidney disease stage 3 or higher, renal failure, chronic uremia, dialysis, or renal transplantation. Depression was defined as an inpatient or outpatient hospital-based depression diagnosis or an antidepressant prescription within 1 year before the

index date. Prescriptions within 2 weeks before the index date were not considered, to avoid misclassifying treatment of acute herpetic neuralgia. Persons with HIV, leukemia, lymphoma, myeloma, HSCT, other immunosuppressive disease, use of oral glucocorticoids, or use of other immunosuppressants were considered to have contraindications for Zostavax use [2].

Codes used to define variables in the study

Variable	Codes
HZ hospital-based diagnoses	**ICD-8**: 053 **ICD-10**: B02
HZ encephalitis	**ICD-10:** B020, G051I
HZ meningitis	**ICD-10:** B021
HZ with other nervous system involvement	**ICD-10:** B022, G051M
HZ ophthalmicus	**ICD-10:** B023, H031F, H131M, H190D, H192D, H192J, H220C
HZ otitis	**ICD-10:** H621B
Disseminated HZ	**ICD-10:** B027
HZ with other complications	**ICD-10:** B028
HZ without complications	**ICD-10:** B029
Unspecified	**ICD-10:** B02 without further specification
Antivirals for HZ	
Acyclovir	**ATC**: J05AB01 (HZ-specific tablet dose 800 mg in package of 35 tablets)
Valacyclovir	**ATC**: J05AB11 (HZ-specific tablet dose: 500 mg)
Famciclovir	**ATC**: J05AB09 (HZ-specific tablet dose: 500 mg)
Specialty code identifying GPs for the validation substudy	Specialist code 80 in the Registry of Health Providers
Rheumatoid arthritis	**ICD-8**: 712.09; 712.19; 712.29; 712.39; 712.59 **ICD-10**: DG737D; DI328A; DI398E; DI418A; DI528A; DJ990; DM05; DM051; DM052; DM053; DM058; DM059; DM060; DM061; DM062; DM063; DM068; DM069; DM080; DM082; DM083; DM084
SLE	**ICD-8**: 734.19 **ICD-10**: DL931; DG058A; DG737C; DI328B; DI398C; DJ991C; DL932; DM32; DN085A; DN164B
IBD	**ICD-8:** 563.01; 563.19; 569.04 **ICD-10:** DK50; DK51; DM074; DM075; DM091; DM092
COPD	**ICD-8:** 491; 492 **ICD-10:** DJ41; DJ42; DJ43; DJ44
Asthma	**ICD-8:** 493 **ICD-10:** DJ45; DJ46
Asthma-related prescription	**ATC:** R03
CKD	**ICD-8:** 584; 792; 997.7; Y95.09

	ICD-10: DL298C; DG638A; DE853B; DT825A; DT825B; DT825C; DT856C; DI120; DI131; DI132; DI770; DN165; DN180; DN183; DN184; DN185; DN188; DN189; DN19; DT824; DT861; DZ49; DZ94; DZ992; DT817E1; **Procedure codes:** BJFD2; BJFZ; BJKB; BUBA2; BUFC1; BWDC5; ZZ0151A; ZZ4341; ZZ4342; ZZ4343; ZZ4346; ZZ4347; ZZ4348; ZZ4350 **Danish surgical codes (old classification):** 57480; 57490; 87409; 87419; 87420; 87430; 87431; 87432; 87440; 92390; 92400; 94300; 94340 **NOMESCO classification codes:** KJAK10; KJAK11; KJAK13; KJAK14; KTJA30; KTJA32; KTJA35; KKAS
Diabetes diagnosis	**ICD-8:** 249–250 **ICD-10:** DE10; DE11; DE12; DE13; DE14; DH360; DO24 (excl. D0244)
Antidiabetics	**ATC**: A10A; A10B (excluding A10BE01); B04AX07; C10AX04
HIV infection	**ICD-8:** 079.83 **ICD-10:** DB20; DB21; DB22; DB23; DB24; DF024; DZ21
Lymphoma	**ICD-8:** 200; 201; 202 **ICD-10:** DC81; DC82; DC83; DC84; DC85; DC86; DC88; DC96
Leukemia	**ICD-8:** 204; 205; 206; 207 **ICD-10:** DC91; DC92; DC93; DC94; DC95
Myeloma	**ICD-8:** 203 **ICD-10:** DC90
HSCT	**ICD-10:** DT860; DZ948C; DZ948 if not DZ948A, DZ948B, DZ948C and if coded as a B-diagnosis or additional diagnosis together with one of the following A-diagnoses C770, C81–C96, D45–D47, D50–D85, D87–D89, T86.0, T86.0A, or T88.8N **Procedure codes:** BOQE; BOQF
OID	**ICD-8:** 284.01; 284.02; 284.08; 284.09; 758.30 **ICD-10**: DD611; DD612; DD613; DD618; DD619; DD81; DD820; DD821; DD821A; DD822; DD83
Inhaled corticosteroids	**ATC**: R03BA*; R03AK06; R03AK07; R03AK08; R03AK09; R03AK10; R03AK11
Oral corticosteroids	**ATC**: H02AB* (excluding injections)
Other immunosuppressants	**ATC**: L01; L04; V02CA01; V02CA02 **Procedure codes:** BOHJ; BWG; BWHB, Or any ATC code for L01*, L04*, V02CA01, or V02CA02 used as additional code in the Patient Registry

Abbreviations: CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; GP=general practitioner; HIV=human immunodeficiency virus; HSCT=hematopoietic stem cell transplantation; HZ=herpes zoster; IBD=inflammatory bowel disease; OID=other immunosuppressive disease; NOMESCO=Nordic Medico-Statistical Committee; SLE=subacute/systemic lupus erythematosus

References

1. Forbes HJ, Bhaskaran K, Thomas SL, Smeeth L, Clayton T, Langan SM. Quantification of risk factors for herpes zoster: population based case-control study. BMJ. 2014;348:g2911.

2. Keating GM. Shingles (herpes zoster) vaccine (zostavax(®)): a review of its use in the prevention of herpes zoster and postherpetic neuralgia in adults aged ≥50 years. Drugs. 2013;73:1227–44.

Supplementary Methods 2. Systematic literature search

On January 6, 2016, we systematically searched MEDLINE (PubMed) and EMBASE to identify European studies on the epidemiology of HZ. We searched for studies with titles including the terms 'zoster' or 'shingles' in combination with 'incidence', 'rate', 'risk', 'epidemiology', 'burden', 'trend', 'trends', 'association' or 'associated'. We also searched reference lists of eligible articles to identify additional relevant studies. The search was part of a review of the literature on the epidemiology of HZ for a PhD thesis of one of the authors (SAJS). This author performed the search, eligibility screening, and data extraction. For the current study, we specifically selected studies that were conducted in Europe and reported age-specific rates of HZ in the primary care and/or the inpatient or outpatient hospital-based setting. We excluded review articles, case reports, and conference abstracts, but aimed to include non-English papers. We identified 1218 papers in MEDLINE and 1154 in EMBASE. After removing duplicates, 1964 papers remained for screening of titles and abstract, 172 of which were deemed eligible for full-text screening. As well, 25 potentially eligible papers were added from reference lists. We were not able to retrieve full-text versions of six non-English studies, which were therefore excluded. These included two studies from the Czech Republic, one from Romania, two from Spain, and one from Germany. Based on their abstracts, the studies from Spain and Germany overlapped with other eligible studies. In this manner, we identified 57 eligible papers that fulfilled eligibility criteria. However, two of these were excluded, because age-specific rates were not reported above age 40 years, thus limiting comparison with our study. Finally, for each country, we selected the study that presented rates based on the most recent and comprehensive dataset that overlapped in calendar time with our study. This left a total of 19 studies for comparison, as listed below. None of the studies in the hospital setting reported rates specifically for outpatient specialty clinics.

Studies reporting age-specific rates including diagnoses of HZ from primary care

- Sweden: Sundström K, Weibull CE, Söderberg-Löfdal K, Bergström T, Sparén P, Arnheim-Dahlström L. Incidence of herpes zoster and associated events including stroke--a population-based cohort study. BMC Infect. Dis. 2015;15:488. (included also hospital diagnoses in the rate)
- United Kingdom: Forbes HJ, Bhaskaran K, Thomas SL, Smeeth L, Clayton T, Langan SM. Quantification of risk factors for herpes zoster: population based case-control study. BMJ. 2014;348:g2911.
- Germany: Hillebrand K, Bricout H, Schulze-Rath R, Schink T, Garbe E. Incidence of herpes zoster and its complications in Germany, 2005-2009. J Infect. 2015;70:178–86. (included also hospitalizations in the rate)
- Belgium: Bilcke J, Ogunjimi B, Marais C, de Smet F, Callens M, Callaert K, et al. The health and economic

burden of chickenpox and herpes zoster in Belgium. Epidemiol. Infect. 2012;140:2096–109.
- Switzerland: Jean-Luc R, Hans-Peter Z. Herpès zoster 1998–2001. Sentinella-Jahresbericht; 2017 Jan.
- France: Gonzalez Chiappe S, Sarazin M, Turbelin C, Lasserre A, Pelat C, Bonmarin I, et al. Herpes zoster: Burden of disease in France. Vaccine. 2010;28:7933–8.
- Italy: Alicino C, Trucchi C, Paganino C. Incidence of herpes zoster and post-herpetic neuralgia in Italy: Results from a three-years population-based study. Hum Vaccin Immunother. 2016;7:1–6.
- Spain: Esteban-Vasallo MD, Gil-Prieto R, Domínguez-Berjón MF, Astray-Mochales J, de Miguel AG. Temporal trends in incidence rates of herpes zoster among patients treated in primary care centers in Madrid (Spain), 2005-2012. J Infect. 2014;68:378–86.
- Slovenia: Socan M, Blasko M. Surveillance of varicella and herpes zoster in Slovenia, 1996-2005. Eurosurveillance. Euro surveillance; 2007;12:13–6.
- The Netherlands: van Lier A, Lugnér A, Opstelten W, Jochemsen P, Wallinga J, Schellevis F, et al. Distribution of Health Effects and Cost-effectiveness of Varicella Vaccination are Shaped by the Impact on Herpes Zoster. EBioMedicine. 2015;2:1494–9.

Studies reporting age-specific rates for hospitalizations with HZ as the primary diagnosis

- Sweden: Studahl M, Petzold M, Cassel T. Disease burden of herpes zoster in Sweden--predominance in the elderly and in women - a register based study. BMC Infect. Dis. 2013;13:586.
- Germany: Ultsch B, Siedler A, Rieck T, Reinhold T, Krause G, Wichmann O. Herpes zoster in Germany: quantifying the burden of disease. BMC Infect. Dis. 2011;11:173.
- The Netherlands: de Melker H, Berbers G, Hahné S, Rümke H, van den Hof S, de Wit A, et al. The epidemiology of varicella and herpes zoster in The Netherlands: implications for varicella zoster virus vaccination. Vaccine. 2006;24:3946–52.
- Belgium: Bilcke J, Ogunjimi B, Marais C, de Smet F, Callens M, Callaert K, et al. The health and economic burden of chickenpox and herpes zoster in Belgium. Epidemiol. Infect. 2012;140:2096–109.
- Spain: Esteban-Vasallo MD, Domínguez-Berjón MF, Gil-de-Miguel A, Astray-Mochales J, Blanco-Ancos LM, Gil-Prieto R. Characteristics of herpes zoster-associated hospitalizations in Madrid (SPAIN) before vaccine availability. J. Infect. 2016;72:70–9.
- Portugal: Mesquita M, Froes F. Hospital admissions for herpes zoster in Portugal between 2000 and 2010. Acta Med Port. 2013;26:531–6.

Studies reporting age-specific rates for hospitalizations with HZ as the primary or a secondary diagnosis

- United Kingdom: Hobbelen PHF, Stowe J, Amirthalingam G, Miller L, van Hoek A-J. The burden of hospitalisation for varicella and herpes zoster in England from 2004 to 2013. J. Infect. 2016;73:241–53.
- France: Gonzalez Chiappe S, Sarazin M, Turbelin C, Lasserre A, Pelat C, Bonmarin I, et al. Herpes zoster: Burden of disease in France. Vaccine. 2010;28:7933–8.
- The Netherlands: de Melker H, Berbers G, Hahné S, Rümke H, van den Hof S, de Wit A, et al. The epidemiology of varicella and herpes zoster in The Netherlands: implications for varicella zoster virus vaccination. Vaccine. 2006;24:3946–52.
- Spain: Gil-Prieto R, Walter S, Gonzalez-Escalada A, Garcia-Garcia L, Marín-García P, Gil-de-Miguel A. Different vaccination strategies in Spain and its impact on severe varicella and zoster. Vaccine. 2014;32:277–83.
- Italy: Gialloreti LE, Merito M, Pezzotti P, Naldi L, Gatti A, Beillat M, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. BMC Infect. Dis. 2010;10:230.

Table S1. Distribution of demographic and diagnostic variables for persons with herpes zoster according to the overall, prescription-based, and hospital-based algorithms, Denmark, 1997–2013. Values are number (%) unless otherwise stated.

Combined *(n=189,025)*	
Women	115,262 (60.98)
Median age (interquartile range), years	64 (54–75)
Age group, years	
40–49	29,912 (15.82)
50–59	42,673 (22.58)
60–69	46,608 (24.66)
70–79	40,069 (21.20)
80–89	24,602 (13.02)
≥90	5161 (2.73)
Prescription-based *(n=181,848)*	
Women	175,088 (63.49)
Median age (interquartile range), years	60 (50–72)
Age group, years	
40–49	65,444 (23.73)
50–59	68,216 (24.74)
60–69	62,172 (22.55)
70–79	47,116 (17.09)
80–89	27,138 (9.84)
≥90	5665 (2.05)
Type of defining antiviral prescription	
Acyclovir	233,487 (84.67)
Valacyclovir	38,565 (13.99)
Famciclovir	3699 (1.34)
Hospital-based *(n=10,690)*	
Women	6232 (58.3)
Median age (interquartile range), years	72 (61–81)
Age group, years	
40–49	847 (7.92)
50–59	1590 (14.87)
60–69	2263 (21.17)
70–79	2849 (26.65)
80–89	2596 (24.28)
≥90	545 (5.10)
Type of contact	
Inpatient diagnosis	6560 (61.37)
Outpatient clinic diagnosis	2693 (25.19)
Emergency room diagnosis	1437 (13.44)
Type of diagnosis	
Primary diagnosis	7471 (69.89)
Secondary diagnosis	3219 (30.11)
Defining diagnosis	
HZ encephalitis	237 (2.22)
HZ meningitis	41 (0.38)
HZ with other nervous system involvement	827 (7.74)
HZ ophthalmicus	1411 (13.20)
HZ otitis	15 (0.14)
Disseminated HZ	204 (1.91)
HZ with other complication	579 (5.42)
HZ without complication	7242 (67.75)
Unspecified	134 (1.25)

Table S2. Risk factors for herpes zoster among cases and matched controls, Denmark, 1997–2013.

	HZ-specific prescriptions					HZ diagnoses				
	Cases, n (%)	Controls, n (%)	Odds ratios (99% confidence interval)*			Cases, n (%)	Control, n (%)	Odds ratios (99% confidence interval)*		
			Model 1	Model 2	Model 3			Model 1	Model 2	Model 3
Total	181,848	909,226	NA	NA	NA	10,690	53,450	NA	NA	NA
Rheumatoid arthritis	3904 (2.15)	11,631 (1.28)	1.70 (1.62–1.78)	1.64 (1.56–1.72)	1.27 (1.20–1.33)	429 (4.01)	796 (1.49)	2.76 (2.36–3.23)	2.56 (2.16–3.02)	1.53 (1.27–1.84)
SLE	432 (0.24)	993 (0.11)	2.18 (1.88–2.53)	1.91 (1.65–2.22)	1.60 (1.37–1.87)	44 (0.41)	37 (0.07)	5.95 (3.34–10.57)	4.25 (2.30–7.86)	2.94 (1.52–5.69)
IBD	2550 (1.40)	9065 (1.00)	1.41 (1.33–1.50)	1.36 (1.29–1.45)	1.29 (1.22–1.37)	179 (1.67)	465 (0.87)	1.94 (1.55–2.44)	1.67 (1.31–2.14)	1.50 (1.16–1.93)
COPD	10,463 (5.75)	38,243 (4.21)	1.40 (1.36–1.44)	1.35 (1.31–1.39)	1.16 (1.12–1.20)	1433 (13.41)	2756 (5.16)	2.89 (2.64–3.17)	2.76 (2.51–3.03)	2.05 (1.83–2.29)
Asthma	2633 (1.45)	9724 (1.07)	1.36 (1.28–1.44)	1.36 (1.29–1.44)	1.18 (1.11–1.26)	164 (1.53)	511 (0.96)	1.62 (1.28–2.05)	1.83 (1.43–2.34)	1.46 (1.12–1.91)
CKD	2519 (1.39)	7463 (0.82)	1.71 (1.61–1.81)	1.45 (1.37–1.55)	1.39 (1.30–1.48)	665 (6.22)	550 (1.03)	6.41 (5.50–7.47)	4.10 (3.44–4.88)	3.66 (3.06–4.38)
Depression	24,156 (13.28)	102,615 (11.29)	1.21 (1.19–1.23)	1.17 (1.15–1.20)	1.16 (1.14–1.19)	1988 (18.60)	6542 (12.24)	1.66 (1.55–1.79)	1.48 (1.36–1.60)	1.44 (1.32–1.56)
Diabetes	13,281 (7.30)	61,291 (6.74)	1.09 (1.06–1.12)	1.05 (1.03–1.08)	1.05 (1.03–1.08)	1154 (10.80)	4093 (7.66)	1.46 (1.34–1.60)	1.34 (1.22–1.48)	1.34 (1.21–1.48)
Type I	339 (0.19)	1460 (0.16)	1.17 (1.00–1.36)	1.12 (0.96–1.31)	1.10 (0.94–1.29)	29 (0.27)	42 (0.08)	3.49 (1.87–6.51)	2.86 (1.46–5.61)	3.04 (1.54–6.01)
Type II	11,758 (6.47)	54,683 (6.01)	1.08 (1.05–1.11)	1.05 (1.02–1.08)	1.05 (1.02–1.08)	1005 (9.40)	3749 (7.01)	1.39 (1.26–1.53)	1.29 (1.16–1.43)	1.29 (1.16–1.43)
Unknown	1184 (0.65)	5148 (0.57)	1.16 (1.06–1.26)	1.11 (1.02–1.20)	1.10 (1.01–1.20)	120 (1.12)	302 (0.57)	2.05 (1.55–2.71)	1.76 (1.30–2.38)	1.72 (1.26–2.34)
Inhaled glucocorticoids	10,747 (5.91)	39,163 (4.31)	1.40 (1.36–1.44)	1.18 (1.14–1.23)	1.24 (1.20–1.28)	983 (9.20)	2359 (4.41)	2.21 (2.00–2.45)	1.38 (1.22–1.57)	1.22 (1.07–1.39)
HIV	293 (0.16)	440 (0.05)	3.34 (2.75–4.06)	3.21 (2.64–3.91)	3.22 (2.65–3.92)	78 (0.73)	10 (0.02)	39.00 (16.39–92.77)	36.97 (15.43–88.57)	37.73 (15.68–90.77)
Leukemia	671 (0.37)	1058 (0.12)	3.18 (2.80–3.62)	2.15 (1.87–2.48)	2.28 (1.99–2.62)	272 (2.54)	77 (0.14)	18.48 (13.15–25.97)	12.69 (8.71–18.50)	11.01 (7.49–16.17)
Lymphoma	1036 (0.57)	1251 (0.14)	4.16 (3.73–4.64)	3.09 (2.76–3.46)	3.46 (3.10–3.87)	447 (4.18)	107 (0.20)	21.41 (16.17–28.36)	16.43 (12.19–22.16)	13.35 (9.82–18.16)
Myeloma	381 (0.21)	334 (0.04)	5.70 (4.70–6.92)	3.23 (2.62–3.97)	3.96 (3.23–4.85)	231 (2.16)	37 (0.07)	31.22 (19.77–49.29)	16.47 (9.87–27.46)	12.32 (7.26–20.92)
HSCT	566 (0.31)	601 (0.07)	4.71 (4.05–5.48)	1.93 (1.62–2.30)	1.97 (1.65–2.34)	292 (2.73)	50 (0.09)	29.74 (19.97–44.29)	2.47 (1.46–4.18)	2.27 (1.35–3.84)
OID	241 (0.13)	440 (0.05)	2.74 (2.23–3.37)	1.60 (1.28–2.00)	1.66 (1.33–2.06)	75 (0.70)	33 (0.06)	11.36 (6.63–19.48)	2.42 (1.19–4.92)	2.38 (1.16–4.88)

Oral glucocorticoids	8011 (4.41)	18,793 (2.07)	2.20 (2.13–2.28)	1.80 (1.73–1.87)	1.92 (1.85–1.99)	1285 (12.02)	1419 (2.65)	5.05 (4.55–5.61)	3.48 (3.09–3.91)	3.10 (2.75–3.50)
Other immunosuppressants	3966 (2.18)	7970 (0.88)	2.53 (2.40–2.66)	1.77 (1.67–1.87)	1.96 (1.85–2.07)	686 (6.42)	417 (0.78)	8.79 (7.45–10.37)	4.05 (3.32–4.93)	3.10 (2.53–3.79)

Abbreviations: CI=confidence interval; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; HSCT=hematopoietic stem cell transplantation; IBD=inflammatory bowel disease; IQR=interquartile range; OID=other cellular immune deficiency; OR=odds ratio; SLE=subacute/systemic lupus erythematosus

*Computed using conditional logistic regression. Model 1 included no other variables. Model 2 included rheumatoid arthritis, SLE, IBD, COPD, asthma, CKD, depression, diabetes (any type), HIV, leukemia, lymphoma, myeloma, HSCT, and OID. Model 3 included, in addition, inhaled glucocorticoids, oral glucocorticoids, and other immunosuppressants. When examining subtypes of diabetes, separate models were run for each subtype instead.

Figure S1. Age-specific rates of herpes zoster with 95% confidence intervals among women (red) and men (blue) overall and in the hospital-based setting, Denmark, 1997–2013. Note different y-axis for hospital diagnosis rate

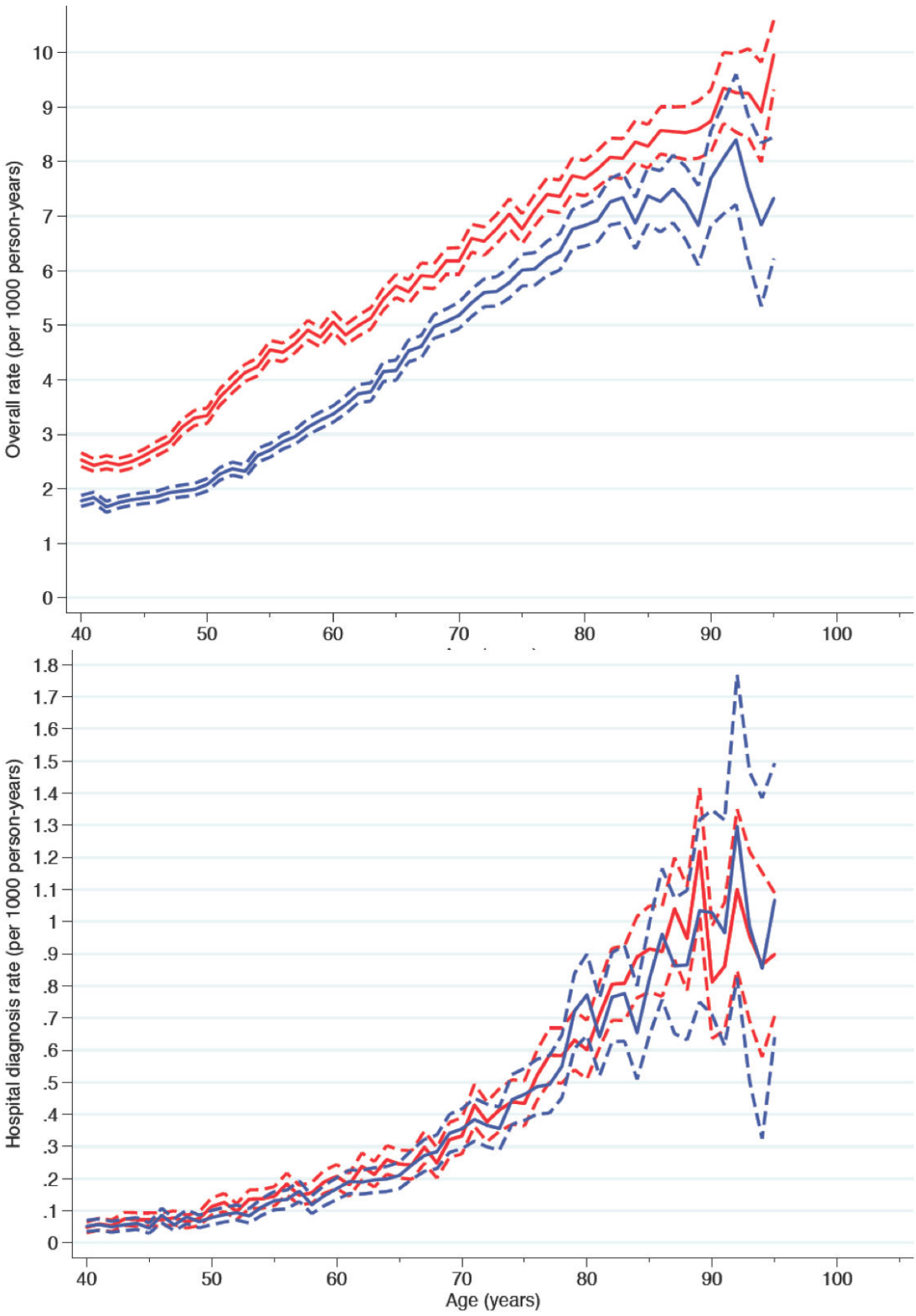
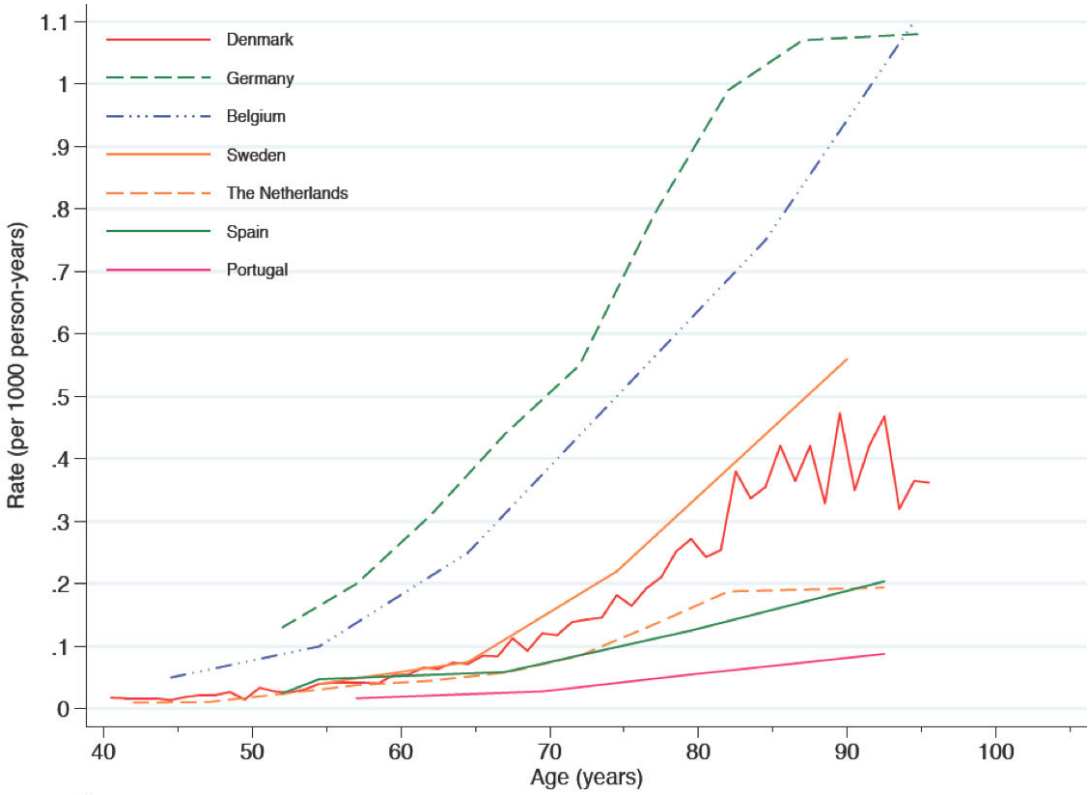
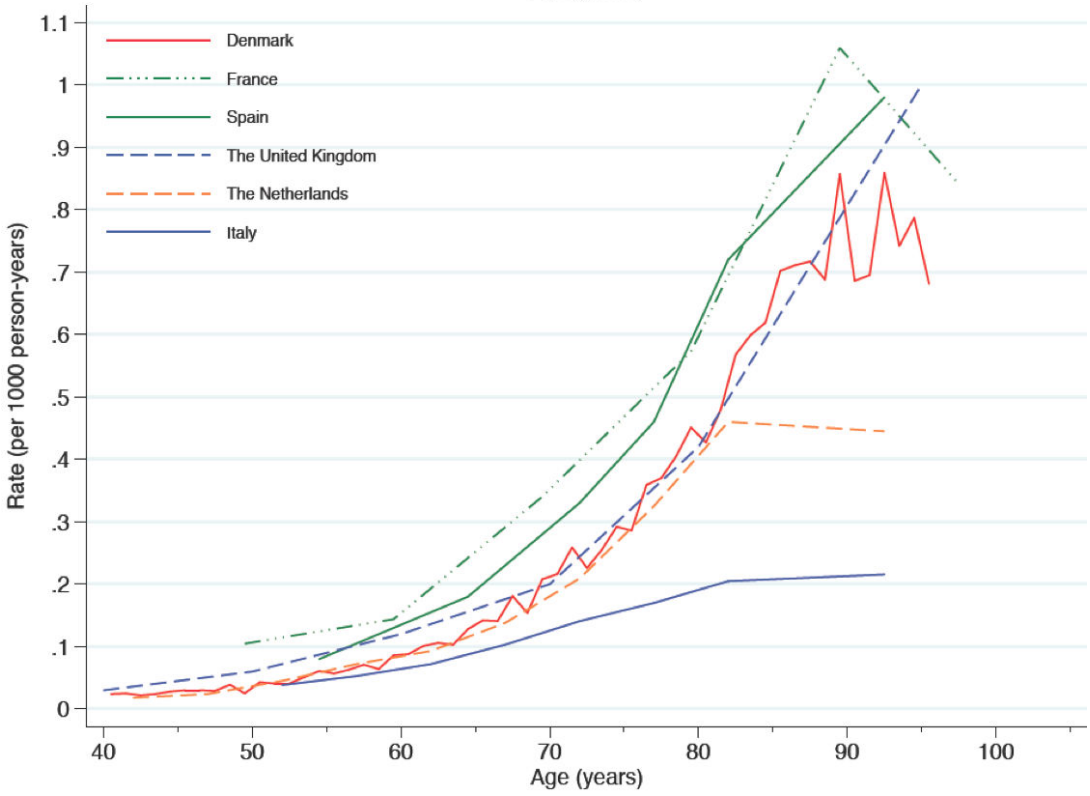


Figure S2. Age-specific rates of hospital admissions with herpes zoster as a primary diagnosis (upper graph) or the primary or a secondary diagnosis (lower graph) in the present study compared with those reported by previous European studies.





Paper II

- **Appendix II**:

Clinical Infectious Diseases

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Partner Bereavement and Risk of Herpes Zoster: Results from Two Population-Based Case-Control Studies in Denmark and the United Kingdom

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Background. Psychological stress is commonly thought to increase the risk of herpes zoster by causing immunosuppression. However, epidemiological studies on the topic are sparse and inconsistent. We conducted 2 parallel case-control studies of the association between partner bereavement and risk of zoster using electronic healthcare data covering the entire Danish population and general practices in the UK Clinical Practice Research Datalink.

Methods. We included patients with a zoster diagnosis from the primary care or hospital-based setting in 1997–2013 in Denmark (n = 190 671) and 2000–2013 in the United Kingdom (n = 150 207). We matched up to 4 controls to each case patient by age, sex, and general practice (United Kingdom only) using risk-set sampling. The date of diagnosis was the index date for case patients and their controls. We computed adjusted odds ratios with 99% confidence intervals for previous bereavement among case patients versus controls using conditional logistic regression with results from the 2 settings pooled using random-effects meta-analysis.

Results. Overall, the adjusted odds ratios for the association between partner bereavement and zoster were 1.05 (99% confidence interval, 1.03–1.07) in Denmark and 1.01 (.98–1.05) in the United Kingdom. The pooled estimates were 0.72, 0.90, 1.10, 1.08, 1.02, 1.04, and 1.03 for bereavement within 0–7, 8–14, 15–30, 31–90, 91–365, 366–1095, and >1095 days before the index date, respectively.

Conclusions. We found no consistent evidence of an increased risk of zoster after partner death. Initial fluctuations in estimates may be explained by delayed healthcare contact due to the loss.

Keywords. bereavement; grief; herpes zoster; shingles; psychological stress.

It is commonly thought that severe psychological stress can provoke reactivation of latent herpesviruses, including the varicella zoster virus, which causes herpes zoster (HZ) [1]. This belief is supported by immunological studies demonstrating activation of the hypothalamic-pituitary-adrenal axis and inhibition of natural killer cell activity, phagocytosis, and cytotoxic T-cell activity in response to stress [1–3]. However, epidemiological data assessing stress as a risk factor for HZ are sparse and inconsistent [4–8].

Five studies have examined the association between negative life events and HZ, with some reporting at least a 40% increase in relative risk up to 4 years after the event [4–7], whereas others report no association [8]. This lack of consistent evidence may be explained by the difficulty of measuring psychological stress, given variation among persons in the types of life events perceived as stressful. Indeed, various measures of stress were employed (eg, health events in partners [8] or the Geriatric Scale of Recent Life Events [5, 6]) in the previous studies.

The death of a loved one is considered extremely stressful [9]. It is likely to affect most persons gravely regardless of coping mechanisms [10], making it a useful model for studying the effects of psychological stress. We therefore examined whether partner bereavement was associated with HZ in 2 parallel case-control studies in Denmark and the United Kingdom.

METHODS

Data Sources

Denmark and the United Kingdom have publicly funded healthcare systems [11, 12]. Primary healthcare is delivered by general practitioners, who act as gatekeepers to specialized secondary care provided at hospitals. Prescription drugs are partially or fully reimbursed, although reimbursement schemes differ slightly between the countries.

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In Denmark, we used nationwide registries to obtain data on all inpatient and outpatient contacts with nonpsychiatric hospitals (the Danish National Patient Registry [13]) and psychiatric hospitals (the Danish Psychiatric Central Research Registry [14]); prescriptions dispensed at community pharmacies (the Danish National Prescription Registry [15]; patients receiving care for diabetes (the Danish National Diabetes Registry [16]); education (the Population Education Registry [17]); and general demographic data, for example, civil status and vital status (the Civil Registration System [18]).

The main data source for the UK study was the Clinical Practice Research Datalink (CPRD), which contains electronic primary healthcare records for approximately 7% of the UK population [19]. Sixty percent of participating practices allow linkage with hospital inpatient data (the Hospital Episode Statistics database [20]) and individual-level social data (the Index of Multiple Deprivation [21]), which were also used in the present study. Further details about the data sources are provided in Supplementary Appendix 1.

The Danish study was approved by the Danish Data Protection Agency (record number: 2013-41-1719). Danish legislation does not require approval by an ethical review board or informed consent from patients for registry-based studies. The British study was approved by the CPRD Independent Scientific Advisory Committee (record number: 15_248) and the London School of Hygiene and Tropical Medicine Ethics Committee (record number: 11219). Study protocols, including complete code lists, are available as supplementary data.

Study Population

We included persons with a first-time diagnosis of HZ recorded in general practice or with a primary (first-listed) hospital-based diagnosis of HZ between 1997 and 2013 in Denmark and between 2000 and 2013 in the United Kingdom. Hospital-based diagnoses were available in both settings. However, while general practitioners in the CPRD register reasons for patient contact using Read Codes, diagnoses of HZ are not recorded in primary care in Denmark. As a surrogate measure for HZ treated in this setting, we therefore used the Danish National Prescription Registry to identify prescriptions for systemic acyclovir, valacyclovir, and famciclovir at tablet doses most likely to represent treatment for HZ (800 mg acyclovir in packages with 35 pills or a 500-mg tablet dose of valacyclovir or famciclovir) [22]. Persons with any previous prescription for 1 of the 3 antivirals were ineligible, because repeated use is more common for competing indications (ie, reactivating herpes simplex). Given that herpes simplex is most frequent in young persons [23], we included only individuals aged ≥40 years in Denmark as well as in the United Kingdom (for comparability). To avoid including patients with long-term HZ-related complications, persons were ineligible if they had any previous diagnosis of postherpetic neuralgia from general practice (not available in Denmark) or the hospital-based setting or if they had a hospital-based HZ diagnosis not recorded as the primary diagnosis for the hospital contact. In the UK study, we also required that persons had been registered with their current general practice for ≥12 months before the index date to exclude past history of HZ recorded shortly after registration [24]. The index date for case patients was the earliest of the following: date of primary care diagnosis (date a relevant antiviral drug was dispensed in Denmark), date of hospital admission, or start of outpatient clinic follow-up.

We individually matched up to 4 population controls to each case patient by age, sex, and general practice (the United Kingdom only) using risk-set sampling [25] from the Civil Registration System in Denmark and from the CPRD in the United Kingdom. We gave preference to controls who were closest in age to the case patient, allowing a 2-month difference in Denmark and up to 1 year in the United Kingdom, where only year of birth was available. Controls were assigned the same index date as their case patient, and we applied the same inclusion criteria. In the United Kingdom, we excluded inactive controls (persons with no consultation record in the CPRD in the period 6 months before to 12 months after the index date) after matching [26]. In the main analysis, case patients and controls were included regardless of partner/civil status. Because the HZ vaccine was introduced in September 2014 in Denmark and in September 2013 in the United Kingdom, the vast majority of study participants were unvaccinated.

Partner Bereavement

The full exposure definitions are summarized in Supplementary Appendix 2. In the Danish study, we identified partners using an algorithm developed by Statistics Denmark, a government-funded institution responsible for collecting, processing, and publishing data for various scientific purposes [27]. The algorithm combines data on civil status, kinship, exact address, birth year, and sex registered in the Civil Registration System to identify partners (married persons, same-sex couples living in a registered partnership, and nonmarried cohabitating couples). Because the personal identifiers for the couple are available, it was possible to accurately identify the vital status of case patients' and controls' current or previous partners.

In the United Kingdom, we adapted a previously described method to identify partners in the CPRD based on the "family number," which identifies persons in a practice who live in the same household or who are otherwise associated (eg, live in the same institution) [28]. Cohabitees were classified as partners if they were persons of the opposite sex, with an age gap of ≤10 years, and with no younger adult in the household within ≤15 years of age of either person in the couple [28]. We applied these age criteria to avoid misclassifying the death of a child

as partner bereavement. We did not consider cohabitees to be partners if the case patient or control had codes in the primary care record indicating residence in a communal establishment before the index date, if both individuals in the couple were aged ≥95 years, and/or if the same family number was used for >10 persons registered with the practice. We used the death date in the deceased partner's primary care record as the date of bereavement.

To explore whether the association between bereavement and HZ depended on whether the death of a partner was unforeseen, we computed their age-adjusted Charlson Comorbidity Index score, in both UK and Danish data. This index assigns 0–6 points to various chronic diseases according to their ability to predict death, with additional points given according to age [29]. Based on the total score, we categorized risk of partner death as low (0–3 points), intermediate (4–6 points), or high (≥7 points). We excluded records within the month before death to avoid including diagnoses coded retrospectively at death (eg, the cause of death). As an alternative measure in the UK study, we also examined primary care and hospital records for terminal disease among partners before time of death (Supplementary Appendix 2).

Statistical Analysis

We used conditional logistic regression to compute unadjusted odds ratios (ORs) associating previous partner bereavement with HZ. We selected 99% confidence intervals (CIs) as a measure of precision and based interpretations on clinical significance of the point estimates rather than dichotomizing to statistical significance according to an arbitrary significance level [30]. Given the risk-set sampling of controls, the ORs provide an unbiased estimate of the incidence rate ratios [25]. In multivariable analyses, we also adjusted for potential risk factors for HZ [26], including previous records of rheumatoid arthritis, systemic/subacute lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, human immunodeficiency virus infection, hematopoietic stem cell or bone marrow transplantation, solid organ transplantation, or other cellular immune deficiency at any time before index date; leukemia, lymphoma or myeloma within 2 years before the index date; and prescription records for oral glucocorticoids, other immunosuppressant drugs, or inhaled glucocorticoids within 90 days before the index date (see Supplementary Appendix 2 for definitions used).

We hypothesized that an increase in risk of HZ would be most pronounced within the first 3 months after bereavement. Within this 3-month period there could further be some variation related to the time from bereavement to decline in immunity and onset of HZ. To detect discrete fluctuations in the OR, we therefore examined the association between HZ and partner bereavement within 0–7, 8–14, 15–30, 31–90, 91–365, 366–1095, or >1095 days before the index date. Persons who had not previously experienced partner death provided the reference in all comparisons. As the Danish and UK studies were designed to resemble each other closely, we pooled the main results using DerSimonian and Lairds' random-effects model [31]. We used the I^2 statistic to estimate the percentage of inconsistency between study estimates that cannot be explained by chance alone [32].

In stratified analyses, we examined whether ORs for bereavement within 0–30 days before the index date depended on risk of partner death (based on their Charlson Comorbidity Index and records of terminal disease), age, or sex. We also determined whether ORs were higher among persons with medical records indicating depression or anxiety within 90 days before the index date, because we hypothesized that bereavement may provoke or exacerbate these conditions [10] and thereby cause HZ [26].

Sensitivity Analyses

We performed several planned sensitivity analyses, described in more detail in Supplementary Appendix 3. Briefly, we first repeated the stratified analyses using a 90-day exposure window. Second, we excluded single subjects from the reference group. Third, we adjusted for individual-level measures of socioeconomic status, as it may be associated both with inequality in life expectancy (and thus probability of partner death) and with timely healthcare seeking for HZ. We used highest level of achieved education in Denmark (available for 90%) and quintiles of the patient-level Index of Multiple Deprivation scores in the United Kingdom (available for 60%). Fourth, in the UK study, we examined the impact of adjusting for smoking status, alcohol consumption, and body mass index. Because data were missing for 12% of subjects in this analysis, we used both a complete-case approach and multiple imputation by chained equations [33]. Valid lifestyle data were not available in the Danish study [34]. Finally, we repeated the Danish analyses after excluding case patients identified based on prescriptions for which the indication code did not state HZ. We did not use indication codes for the main analyses due to incomplete and unspecific coding. We performed all analyses using the Stata statistical software package (StataCorp).

RESULTS

We included 190 671 HZ case patients and 762 684 controls in the Danish study and 150 207 HZ case patients and 576 878 controls in the UK study (Figure 1). Median age was approximately 65 years, and >60% were women (Table 1). The relative distribution of HZ risk factors among case patients versus controls was very similar in the 2 studies, although absolute numbers differed, particularly for asthma, chronic kidney disease, and inhaled glucocorticoids (Supplementary Appendix 3).

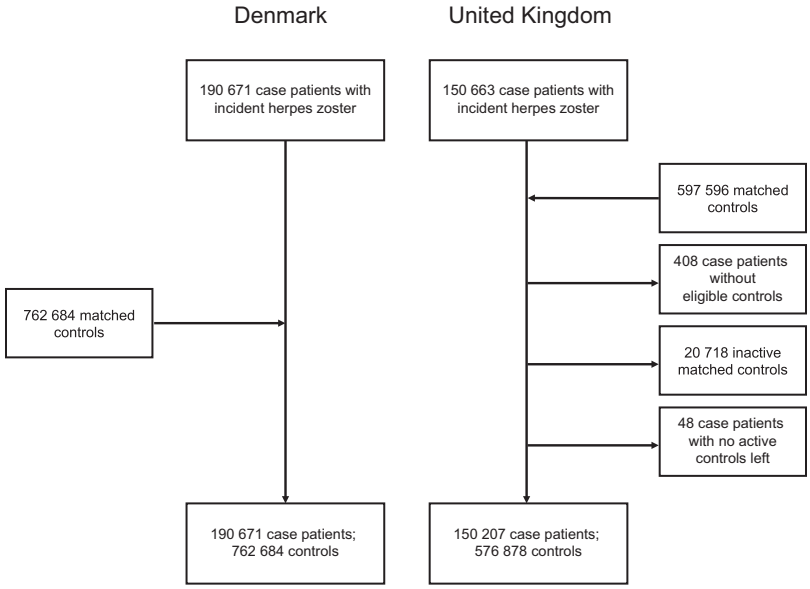

Figure 1. Flowchart for the studies. Inclusion criteria for case patients and controls were age ≥40 years; no previous Read Code or *International Classification of Diseases*, 10th revision, code for postherpetic neuralgia; no previous prescription for systemic acyclovir, valacyclovir, or famciclovir (Denmark only); and registration with current general practice for ≥12 months before the index date (United Kingdom only).

The adjusted OR for any previous partner bereavement was 1.05 (99% CI, 1.03–1.07) in Denmark and 1.01 (.98–1.05) in the United Kingdom (Table 2). Unadjusted and adjusted ORs were very similar. The I^2 statistics from the meta-analysis were <20% within 0–90 days before the index date (Figure 2). Although we found evidence of statistical heterogeneity for remaining exposure windows, the effect estimates were similar, and neither study supported a substantial increase in relative risk. We therefore combined the estimates for all periods. The pooled adjusted ORs were 0.72 (99% CI, .47–1.12), 0.90 (.55–1.46), 1.10 (.83–1.45), 1.08 (.95–1.23), 1.02 (.91–1.14), 1.04 (1.00–1.10), and 1.03 (.98–1.06) within 0–7, 8–14, 15–30, 31–90, 91–365, 366–1095, and >1095 days before the index date, respectively. In both settings, the suggestion of an initial decrease in the OR

Table 1. Distribution of Matching Factors Among Herpes Zoster Case Patients and Controls

	Denmark, No. (%)[a]		United Kingdom, No. (%)[a]	
Factor	Case Patients (n = 190 671)	Controls (n = 762 684)	Case Patients (n = 150 207)	Controls (n = 576 878)
Sex				
Female	125 526 (65.8)	502 104 (65.8)	90 501 (60.3)	354 057 (61.4)
Male	65 145 (34.2)	260 580 (34.2)	59 706 (39.7)	222 821 (38.6)
Age at index date, median (IQR), y	64 (53–75)	64 (53–75)	65 (55–75)	65 (55–75)
Age group at index date				
40–49 y	34 838 (18.3)	139 352 (18.3)	20 844 (13.9)	77 009 (13.3)
50–59 y	41 898 (22.0)	167 592 (22.0)	33 632 (22.4)	127 508 (22.1)
60–69 y	45 662 (23.9)	182 648 (23.9)	38 437 (25.6)	150 110 (26.0)
70–79 y	39 264 (20.6)	157 056 (20.6)	34 767 (23.1)	136 694 (23.7)
80–89 y	23 968 (12.6)	95 872 (12.6)	19 454 (13.0)	75 566 (13.1)
≥90 y	5041 (2.6)	20 164 (2.6)	3073 (2.0)	9991 (1.7)
Socioeconomic status (practice level)				
1 (least deprived)	…	…	29 889 (19.9)	114 855 (19.9)
2	…	…	29 529 (19.7)	113 395 (19.7)
3	…	…	32 306 (21.5)	124 101 (21.5)
4	…	…	30 580 (20.4)	117 216 (20.3)
5 (most deprived)	…	…	27 903 (18.6)	107 311 (18.6)

Abbreviation: IQR, interquartile range.

[a]Data represent No. (%) of case patients or controls, unless otherwise specified.

Table 2. Odds Ratio for Association Between Partner Bereavement and Herpes Zoster

	Denmark				United Kingdom			
Bereavement Status	Case Patients, No. (%)	Controls, No. (%)	Unadjusted OR (99% CI)	Adjusted OR (99% CI)[a]	Case Patients, No. (%)	Controls, No. (%)	Unadjusted OR (99% CI)	Adjusted OR (99% CI)[a]
Never bereaved	157 076 (82.4)	633 082 (83.0)	Reference	Reference	141 774 (94.4)	544 495 (94.4)	Reference	Reference
Bereaved, by duration of bereavement								
Total	33 595 (17.6)	129 602 (17.0)	1.06 (1.04–1.08)	1.05 (1.03–1.07)	8433 (5.6)	32 383 (5.6)	1.01 (.98–1.05)	1.01 (.98–1.05)
0–7 d	26 (0.01)	159 (0.02)	0.66 (.38–1.15)	0.67 (.38–1.15)	16 (0.01)	77 (0.01)	0.81 (.40–1.64)	0.82 (.40–1.67)
8–14 d	31 (0.02)	126 (0.02)	1.00 (.60–1.68)	1.03 (.61–1.73)	13 (0.01)	74 (0.01)	0.69 (.32–1.50)	0.69 (.32–1.50)
15–30 d	90 (0.05)	367 (0.05)	1.00 (.73–1.35)	1.01 (.74–1.37)	52 (0.03)	165 (0.03)	1.24 (.82–1.87)	1.26 (.84–1.91)
31–90 d	343 (0.2)	1273 (0.2)	1.09 (.94–1.28)	1.10 (.94–1.29)	171 (0.1)	629 (0.1)	1.06 (.85–1.32)	1.05 (.84–1.32)
91–365 d	1572 (0.8)	5977 (0.8)	1.07 (.99–1.15)	1.07 (.99–1.15)	746 (0.5)	2956 (0.5)	0.98 (.88–1.09)	0.98 (.88–1.09)
366–1095 d	3989 (2.1)	15 322 (2.0)	1.06 (1.01–1.11)	1.06 (1.01–1.11)	1755 (1.2)	6712 (1.2)	1.02 (.95–1.09)	1.02 (.95–1.09)
>1095 d	27 544 (14.4)	106 378 (13.9)	1.06 (1.03–1.08)	1.05 (1.03–1.07)	5680 (3.8)	21 770 (3.8)	1.02 (.97–1.06)	1.01 (.97–1.05)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, human immunodeficiency virus infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

observed within 14 days before the index date was followed by a compensatory increase within 15–90 days.

We found no substantial variation in estimates after stratifying by risk of partner death, age, sex, or recent depression/anxiety (Figure 3 and Supplementary Appendix 3). However, meaningful comparisons were hampered by very wide CIs. Results were robust in all sensitivity analyses (Supplementary Appendix 3).

DISCUSSION

This large population-based study using data from Denmark and the United Kingdom found no evidence of a substantially increased relative risk of HZ after partner bereavement. Data from the 2 settings showed similar distribution of well-known risk factors for HZ and effect estimates of similar magnitude for risk of HZ after bereavement.

Our findings corroborate a recent self-controlled case series [8]. Among 39 811 persons experiencing death or an intensive care unit stay lasting >14 days for a previously healthy spouse (insurance cobeneficiaries within 5 years of age and of opposite sex), 59 persons were diagnosed with HZ within the following 90 days, compared with 78 in the control period 31–120 days before exposure, yielding an incidence ratio of 0.76 (95% CI, .54–1.06). Furthermore, the proportion of outpatient healthcare contacts attributed to HZ was not higher than in the control period (relative risk 0.99; 95% CI, .70–1.39). In contrast, in 3 case-control studies, which included 101–389 HZ case patients and 101–511 controls, ORs ranged between 2.64 and 3.40 for self-reported negative life events in the previous 3–6 months [4, 5, 7]. Similarly, in a cohort study of 4162 elderly volunteers, an increased hazard ratio of HZ (1.38; 95% CI, .96–1.97) was observed among persons who reported negative life events in the prior 1–4 years [6]. The discrepancy between the results from these interview-based studies and our study, as well as the previous self-controlled case series, may be explained by important methodological differences, including use of aggregate measures for negative life events [4–7], potential self-selection bias [4–7], lack of interviewer blinding [4, 5, 7], potential recall bias [4, 5, 7], and limited sample sizes [4–7].

Immunological studies show that bereavement is associated with functional cellular immune deficiency [3]. Our study suggests that this effect may not be clinically significant for triggering HZ, because the overall upper confidence limit was only 7% in Denmark and the early fluctuations in ORs are compatible with delayed healthcare seeking among bereaved persons. Nevertheless, it is possible that other types of psychological stress, such as that associated with psychiatric illness, elicit different immune responses than those observed after the, predominantly acute, stress of partner bereavement [3]. For example, it has been demonstrated that persons with major depression have reduced cell-mediated immunity against the varicella zoster virus [35–37].

Major strengths of our study include the large study size, use of prospectively collected data from 2 separate tax-supported healthcare systems, and availability of detailed data on temporality of exposure and outcome. However, several limitations need to be considered. We believe that delayed healthcare contact immediately after loss explains the potential transient decrease in the ORs within 14 days after bereavement. We anticipated that such delay could introduce bias in the Danish study, because patients who present late with HZ may not be prescribed antivirals [22], thus omitting them from study inclusion. Another concern for the prescription-based algorithm is misclassification of herpes simplex, which might be provoked

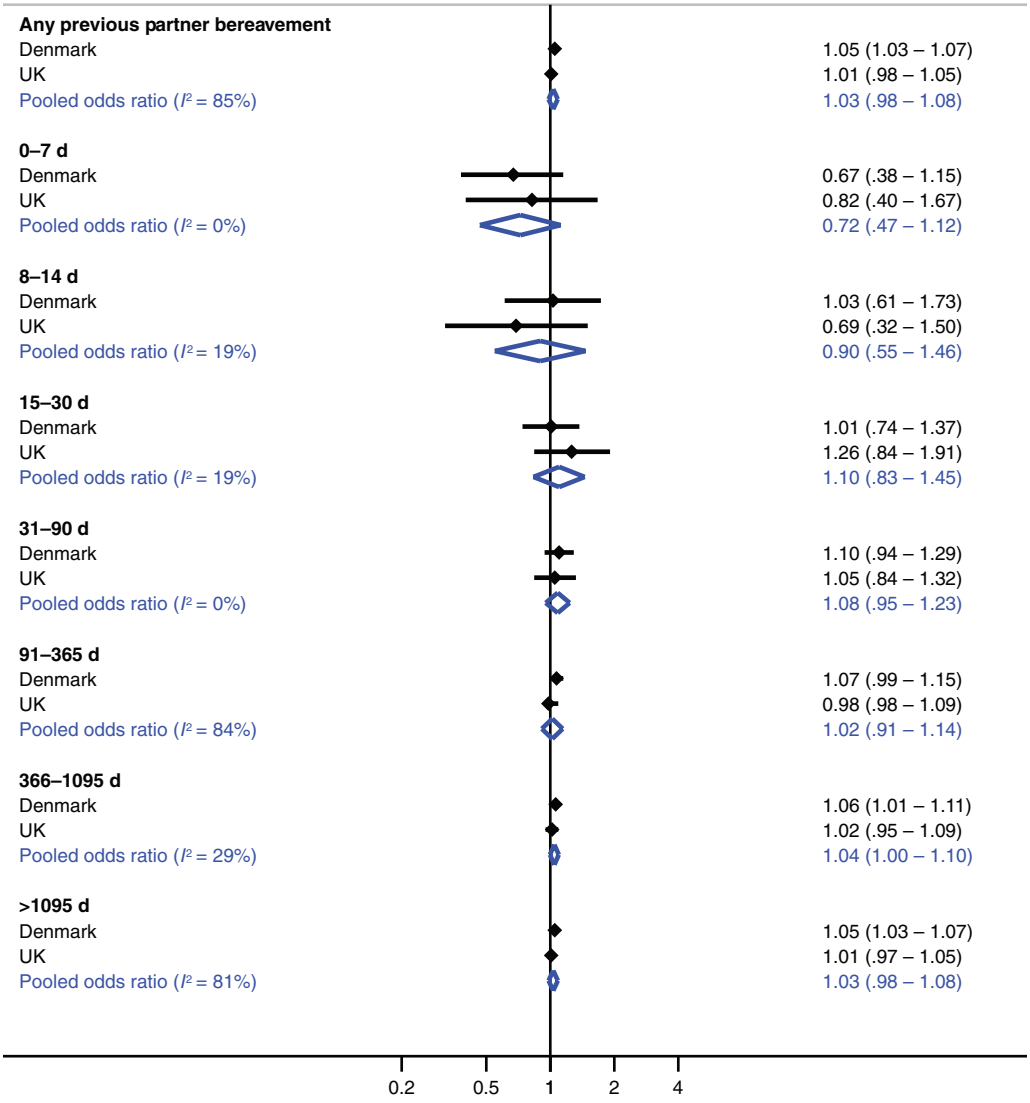

Figure 2. Pooled adjusted odds ratios (99% confidence intervals) from meta-analysis of the association between partner bereavement and herpes zoster in the Danish and UK studies. Odds ratios were adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, human immunodeficiency virus infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

by acute stress [1]. Nevertheless, the similarity between results observed in Denmark and the United Kingdom, including the initial decrease in the OR, suggests that such these biases are negligible.

Misclassification of partner bereavement is possible, in particular in the United Kingdom where data used for identifying partners were less detailed than in Denmark. Use of the general practice family number to identify cohabitating persons may have affected the completeness of our algorithm, as some partners may not be registered with the same general practice. Nevertheless, our results remained robust after excluding single persons from the reference group. Furthermore, the prevalence of previous bereavement was remarkably similar in the Danish and UK data. The only difference was a lower prevalence in the United Kingdom >1 year before the index date, which is consistent with the shorter observation period in the CPRD.

A previous study reported that, according to contemporary national representative household surveys in England, 99% of cohabitating persons aged ≥60 years who are of the opposite sex and have an age difference of <10 years identify themselves as partners [28]. Although these data support a high accuracy of our algorithm, some couples may have represented cohabitating friends or siblings. Still, such misclassification would capture bereavement of a significant person in someone's life, which is also likely to be stressful.

Finally, imprecise estimates limited identification of effect measure modification by the partner's risk of death. Expectation of death is also difficult to categorize and associated psychological distress could depend on the type of chronic disease [10].

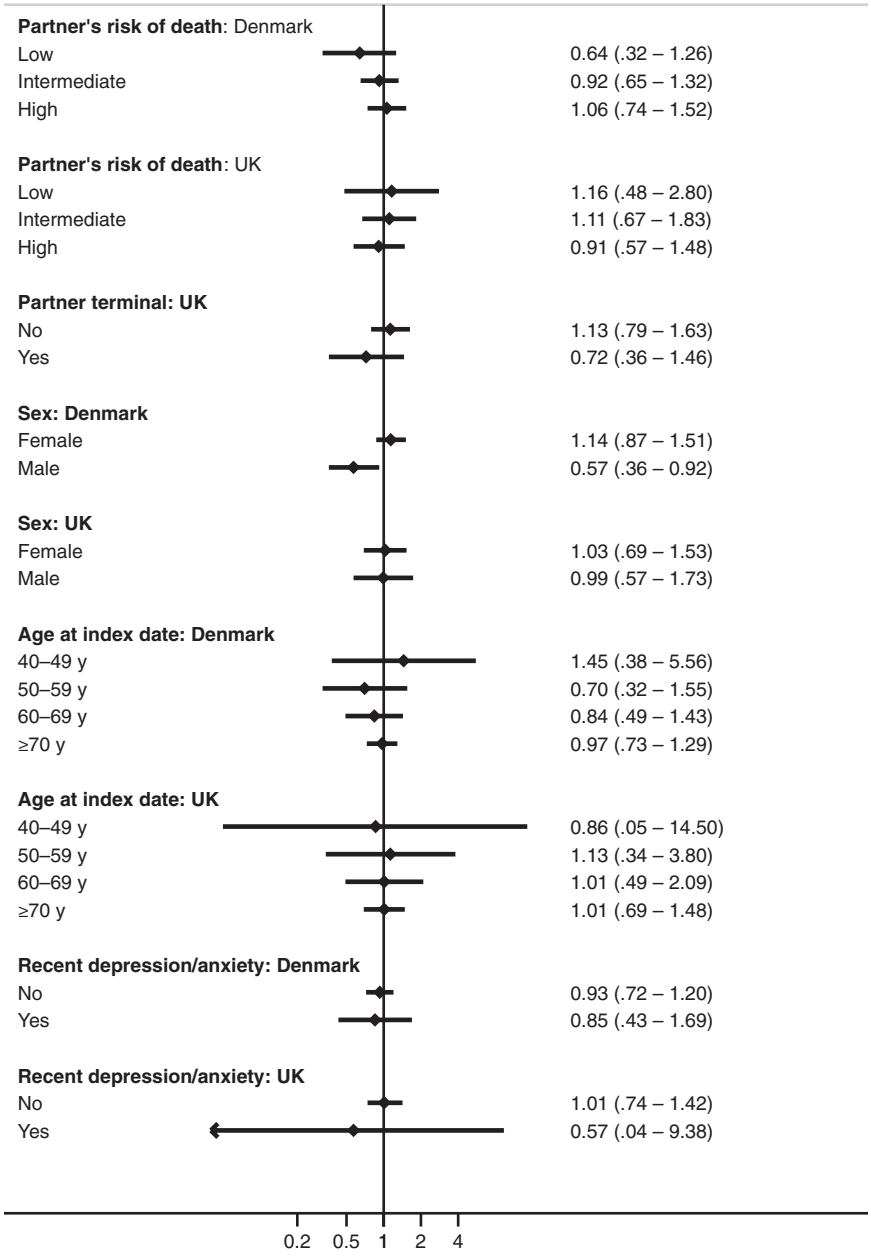

Figure 3. Adjusted odds ratios (99% confidence intervals) for herpes zoster among persons experiencing partner bereavement within the previous 30 days compared with those who had never been bereaved, according to subgroups based on partner's risk of death, sex, age at index date, and recent diagnosis of depression or anxiety. Odds ratios were adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, human immunodeficiency virus infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukaemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids. The partner's risk of death was computed using the age-adjusted Charlson Comorbidity Index score and categorized as low (0–3 points), intermediate (4–6 points), or high (≥7 points).

Furthermore, because the majority of partners were considered at intermediate or high risk of death, the time of bereavement may not mark the beginning of the stressful period.

In conclusion, we found no evidence of a substantial increase in the risk of HZ after partner bereavement. The observed decrease in the relative risk of HZ within 14 days after bereavement followed by corresponding increased risks within subsequent months is compatible with delayed healthcare contact due to the loss.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. All authors participated in designing the study. Analyses were performed by S. A. J. S. for the UK study and by H. S. P. (sampling and initial data management) and S. A. J. S. (final data management

and analyses) for the Danish study. All authors participated in the discussion and interpretation of the results. S. A. J. S. wrote the initial manuscript draft. All authors critically revised the manuscript for intellectual content and approved the final version. S. A. J. S. is the guarantor.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the UK Department of Health.

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Supplementary Appendix 1. Additional details about settings and data sources

Description of Danish data sources

Denmark has a population of approximately 5.6 million inhabitants who have unfettered access to education and medical and social service [1]. There is a long tradition for keeping records of residents' utilization of these services in various nationwide databases. Because data is recorded at the individual-level using the unique civil personal register (CPR) number assigned to all residents at birth or upon immigration, details regarding several aspects of life can be linked accurately to perform epidemiologic studies [1].

The Danish National Patient Registry records data for the Danish hospital sector, including data on all admissions to non-psychiatric hospitals with nationwide coverage since 1978, admissions to psychiatric wards since 1994, and visits to all outpatient hospital-based specialty clinics and emergency rooms since 1994 [2]. Admissions to psychiatric wards between 1970 and 1994 are available in the Danish Psychiatric Central Registry, which was merged with the Danish National Patient Registry in 1995 [3]. These hospital registries include data pertaining to the patient (eg, the CPR number), dates of admission and discharge or start and end of outpatient follow-up, the primary diagnosis, any relevant secondary diagnoses, surgical procedures, other treatments (eg, cancer treatments and psychotherapy) and examinations [2]. The treating physician is responsible for recording relevant diagnoses and treatments at the time of discharge, outpatient contact or surgery. Diagnoses are classified according to the *International Classification of Diseases*, 8th revision (ICD-8) until the end of 1993 and the 10th revision (ICD-10) thereafter. Surgical procedures are coded according to a Danish classification (1977 through 1995) and a Danish version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (from 1996 on).

The Danish National Prescription Registry provides information on prescription drugs since 1995 [4]. Each time a prescription is filled at the pharmacy, the patient's CPR number, the date, the number of packets/units and the Nordic article number of the dispensed product is recorded and

transferred electronically to the registry [4]. The Nordic article number encodes the name, Anatomical Therapeutic Chemical code, the number of tablets or units, numerical strength per tablet or unit and formulation of the drug. Indications and instructions for use are recorded, albeit incompletely, since 2004. In the present study, case selection commenced on January 1, 1997 and continued until December 31, 2013. This ensured that all study participants had at least two years of prescription history without any antiviral prescriptions, thus reducing the chance of including treatment for reactivating herpes simplex infections.

The Danish National Diabetes Registry combines data from several nationwide registries to identify patients receiving care for diabetes since 1995 [5]. The registry population includes individuals with a diagnosis of diabetes in the Danish National Patient Registry; registration of chiropody (reimbursable for diabetics), ≥5 blood-glucose measurements in a 1-year period, or ≥2 yearly blood-glucose measurements in five consecutive years in the National Health Service Register; or ≥2 prescriptions for any oral anti-diabetic drug or ≥2 prescriptions for insulin in the Danish National Prescription Registry [5].

The Civil Registration System includes data on age, sex, address and vital statistics for the entire Danish population since 1968 [1]. The registry also contains data on civil status (married, divorced, widow or widower, registered partnership, or dissolved registered partnership), CPR number of spouse or registered partner, and CPR numbers of children. As the Civil Registration System includes data on all residents, it facilitated selection of population controls for the present case-control study.

We linked all registries on the secure servers at Statistics Denmark — the central authority on Danish statistics, which collects, processes, and publishes information relating to the Danish society. Statistics Denmark also collects data from Danish education registries, such as the Population Education Registry [6], which we also included in the present study.

Description of British data sources

The UK has a population of approximately 61 million inhabitants. As in Denmark, tax-supported medical care is provided free at the point of delivery. However, while Denmark has a long tradition of recording especially hospital contacts, the UK has well established primary care databases [7,8]. One of these databases is the Clinical Practice Research Datalink (CPRD), which was used in the current study [8]. The CPRD was established as a smaller dataset in London in 1987 and was expanded to become the General Practice Research Database in 1993 and finally the CPRD in 2012 [8]. It currently holds data on over 11 million patients from almost 700 practices across the UK. Approximately 4.4 million patients (7% of the UK population) are considered to be active (alive and currently registered) and to have data that meet quality standards put forth by the database. These standards include primarily checks for non-missing data for core variables such as registration dates, birth year, and sex. Participating practices provide electronic health record data to the CPRD through secure servers on a monthly basis. Data collected include various symptoms and diagnoses, tests, health-related behaviours (e.g., smoking status) and anthropometric data, written prescriptions, immunizations and referrals to secondary care. General practice staff are responsible for recording data at the time of patient encounter, using mainly Read codes. The Read code system is a clinical classification system used in general practice in the UK and includes over 96 000 codes hierarchically grouped. Read codes are also converted to medical codes by CPRD. Written prescriptions are coded using the Multilex Product Dictionary, which is translated into product codes.

Sixty percent of practices in the CPRD participate in a linkage scheme, which enables linkage of the primary healthcare records to other data sources, such as the Hospital Episode Statistics database and the Index of Multiple Deprivation [8]. The Hospital Episode Statistics Database was established in 1987 and includes hospitalization data for inpatients treated at National Health Service hospitals in the UK [9]. Linked data are available since 1997. Primary and secondary diagnoses for

the admission are coded using the ICD-10 system and the OPCS (Office of Population and Censuses and Surveys) Classification of Interventions and Procedures version 4 is used to record operations, procedures and interventions. Coding based on hand-written clinical notes is typically outsourced to clinical coders hired by the NHS. Reliable data on contacts to outpatient hospital clinics are not available.

The Index of Multiple Deprivation records data on socioeconomic status at the practice and patient level using quintiles of the Index of Multiple Deprivation Score [10]. This index measures the level of deprivation in small geographical areas (with around 1 500 inhabitants) called the lower layer super output areas. The patient level score is assigned by mapping the home postcode to these areas. The deprivation score is computed by weighing 38 separate indicators within seven domains of deprivation, such as income, employment, crime and living environment. Deprivation increases with increasing score. In the current study, we used the Indices of Deprivation version 2010. Practice level scores were controlled for indirectly through matching by practice and are available for all participating practices in the 2010 dataset.

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Supplementary Appendix 2. Variable definitions

The exposure definitions are described in detail in Table 2a below, including the definitions for risk of partner's death. The Danish Civil Registration System contains exact addresses and kinship status (the unique civil personal register number of parents, siblings and children) for the entire population. This information made it possible to deduce with greater precision the relationship between persons living in the same household, compared to the UK study, which had only information on the age and sex of persons sharing a family practice number. Because of the more detailed data available in Denmark, we were more confident in using an algorithm allowing an age difference of up to 15 years between persons, whereas we included persons with a 10-year age difference or less in the UK. We did not consider consultations for partner bereavement, because such records may depend on health seeking behavior. Among those identified as bereaved by our algorithm in the UK study, only 10% had a recorded consultation for partner bereavement within the subsequent year, suggesting that bereavement codes were too incomplete to meet our study objective. Furthermore, we assumed that basing the timing of partner death on consultations for partner bereavement would be less accurate than that derived from our algorithm.

We used previously described methods to identify risk factors for herpes zoster [1], with minor modifications. We considered records of rheumatoid arthritis, systemic/subacute lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes (type I, type II or unknown type), chronic kidney disease, human immunodeficiency virus infection, hematopoietic stem cell or bone marrow transplantation, solid organ transplantation or other cellular immune deficiency (e.g., primary immunodeficiency) ever before the index date; any record of leukemia, lymphoma or myeloma within two years before the index date; and any prescription records of oral glucocorticoids, other immunosuppressant drugs (e.g., methotrexate or chemotherapy) or inhaled glucocorticoids within 90 days before the index date. The definition of chronic kidney disease included codes for chronic kidney disease stage 3 or higher, renal failure,

chronic uremia, dialysis or renal transplantation. Solid organ transplantation included other types of organ transplants (not renal transplants). For chronic obstructive pulmonary disease, we included diagnoses of chronic bronchitis and emphysema and required that patients were aged 35 years or older at first diagnosis [2]. To capture active asthma, we required that patients with a record of asthma also had an asthma-related prescription within the year before index date. Asthma patients were also required not to be classified as having chronic obstructive pulmonary disease. In the UK study, we defined any history of diabetes as (1) a definite diabetes diagnosis, (2) a possible diagnosis if followed by subsequent antidiabetic prescription or (3) two or more antidiabetic prescriptions (except women treated with metformin alone at age 20 to 39 years, as that may represent treatment of polycystic ovarian syndrome). In the Danish study, we used the Danish National Diabetes Registry, which uses a similar algorithm (see S1 Appendix). Because the Danish National Diabetes Registry does not differentiate between types of diabetes [3] and due to difficulties in identifying the type of diabetes using diagnosis codes in primary care [4], we adjusted for any type of diabetes in analyses. However, for descriptive purposes, we aimed to classify the type of diabetes as type I, type II, or unknown based on information on age at first record, age at first treatment and type of treatment, as in previous CPRD studies [1,5]. We defined type I diabetes as (1) age at first diagnosis $\leq$35 years and exclusive treatment with insulin prior to index date or (2) $\geq$2 insulin prescriptions at age $\leq$35 years but no diabetes diagnosis. Type II diabetes was defined as (1) age at first diabetes diagnosis >35 years or (2) exclusive treatment with oral anti-diabetics at age >35 years. We classified remaining patients with diabetes as having unknown type.

We also identified recent diagnoses of depression or anxiety. Previous studies demonstrate an increase in the use of symptoms of depression rather than diagnoses in electronic health records from primary care following the introduction of the Quality Outcomes Framework [6]. To accommodate this trend, we included both diagnoses and symptoms of depression from the Clinical Practice Research Datalink. In the Danish data, we supplemented with prescription records for

antidepressants to capture conditions treated in general practice [7]. We excluded tricyclic antidepressant prescriptions, because they are also used to treat neuralgia and insomnia.

We included data on patient-level socioeconomic status, measured as highest achieved education in Denmark (short [≤10 years], medium [>10–15 years] or long [>15 years]) and quintiles of the Index of Multiple Deprivation score in the UK.

We used diagnosis codes as well the additional details file in the Clinical Practice Research Datalink to retrieve data on smoking status (current smoker, ex-smoker, non-smoker) and alcohol consumption (current drinker, ex-drinker, non-drinker). We used only the additional details file for the calculation of body mass index (BMI), as medical Read codes are rarely used to record this information. Per convention, we categorized BMI according to the World Health Organization's classification as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (≥30 kg/m^2) [8]. The categorization of the lifestyle variables was pragmatically based on status recorded closest to the index date. When possible, we used the nearest record within –1 year to +1 month, +1 months to +1 years, before –1 year, or within +1 year from index date, listed in the order of priority [1].

The data sources used to define each variable are shown in Table 2b. Codes used to identify herpes zoster cases are shown in Table 2c. Code lists for remaining study variables are available in the study protocols (see Supplementary Appendices 4 and 5).

Table 2a. Exposure definitions used in Danish and UK studies on the association between partner bereavement and herpes zoster

	Denmark	The UK
Partners	1) Married persons 2) Persons in a registered partnership 3) Cohabitating persons, definition 1: • Exact same address • ≥1 cohabitating common child 4) Cohabitating persons, definition 2: • Exact same address • No cohabitating common children (except step children) • Opposite sex • Age difference of <15 years • Not closely related based on patient identifiers for children and parents • No other adults living on the same address	Persons who fulfil all the following criteria: • Same family practice number (people living in the same household or who are otherwise associated) • Opposite sex • Age difference of ≤10 years • No person in the household within 15 years of either of the couple Except if ≥1 of the following: • Case/control has a code indicating residence in a communal establishment before the index date • Both persons in the couple are aged ≥95 years • The family practice number is used for >10 persons
Death	Date of partner death in the Civil Registration System	Date of partner death in the Clinical Practice Research Datalink
Age-adjusted Charlson Comorbidity Index	Records in the Danish National Patient Registry and the Danish National Diabetes Registry at 1 month before the date of death	Records in the Clinical Practice Research Datalink and the Hospital Episodes Statistics database at 1 month before the date of death
Terminal disease	Not available	Records for e.g. delivery of end of life care or terminal illness in the Clinical Practice Research Datalink and the Hospital Episodes Statistics database

Table 2b. Overview of data sources used to define patient characteristics

Variable	Denmark	The UK
Rheumatoid arthritis	ICD-8 and ICD-10 codes in the Patient Registry	Read codes in CPRD; ICD-10 codes in HES
Systemic/subacute lupus erythematosus	ICD-8 and ICD-10 codes in the Patient Registry	Read codes in CPRD; ICD-10 codes in HES
Inflammatory bowel disease	ICD-8 and ICD-10 codes in the Patient Registry	Read codes in CPRD; ICD-10 codes in HES
Chronic obstructive pulmonary disease	ICD-8 and ICD-10 codes in the Patient Registry	Read codes in CPRD; ICD-10 codes in HES
Asthma	ICD-8 and ICD-10 codes in the Patient Registry and ATC codes in the Prescription Registry	Read and product codes in CPRD; ICD-10 codes in HES
Diabetes	Inclusion in the National Diabetes Registry; ICD-8 and ICD-10 codes in the Patient Registry and ATC codes in the Prescription Registry for subtyping	Read and product codes in CPRD; ICD-10 codes in HES
Chronic kidney disease	ICD-8 and ICD-10, surgery and treatment codes in the Patient Registry	Read codes in CPRD; ICD-10 and OPCS codes in HES
Human immunodeficiency virus infection	ICD-8 and ICD-10 codes in the Patient Registry	Read codes in CPRD; ICD-10 codes in HES
Hematopoietic stem cell or bone marrow transplantation	ICD-10 codes and treatment codes in the Patient Registry	Read codes in CPRD; ICD-10 and OPCS codes in HES
Solid organ transplantation	ICD-8 and ICD-10 codes and surgery codes in the Patient Registry	Read codes in CPRD; ICD-10 and OPCS codes in HES
Other cellular immune deficiency	ICD-8 and ICD-10 codes in the Patient Registry	Read codes in CPRD; ICD-10 codes in HES
Leukemia	ICD-8 and ICD-10 codes in the Patient Registry	Read codes in CPRD; ICD-10 codes in HES
Lymphoma	ICD-8 and ICD-10 codes in the Patient Registry	Read codes in CPRD; ICD-10 codes in HES
Myeloma	ICD-8 and ICD-10 codes in the Patient Registry	Read codes in CPRD; ICD-10 codes in HES
Oral glucocorticoids	ATC codes in the Prescription Registry	CPRD product codes
Other immunosuppressant drugs	Treatment codes in the Patient Registry; ATC codes in the Prescription Registry	Read codes in CPRD; ICD-10 and OPCS codes in HES
Inhaled glucocorticoids	ATC codes in the Prescription Registry	CPRD product codes
Depression and anxiety	ICD-8 and ICD-10 codes in the Patient Registry and the Psychiatric Central Registry; ATC codes in Prescription Registry	Read codes in CPRD; ICD-10 codes in HES
Socioeconomic status	Population Education Registry	IMD 2010, providing data on both individual and practice level
Smoking status	Not available	Read codes and additional file data (entity type 4) in CPRD; ICD-10 codes in codes in HES
Alcohol consumption	Not available	Read codes and additional file data (entity type 5) in CPRD; ICD-10 codes in HES
Body mass index	Not available	Additional file data (entity types 104 and 140) in CPRD

Abbreviations: ATC = Anatomical Therapeutic Chemical; CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics Database; ICD = International Classification of Diseases

Table 2c. Codes used to identify herpes zoster cases. All lower level codes are included unless stated otherwise

Denmark	
Hospital diagnoses of herpes zoster	ICD-8: 053; ICD-10: B02 (except B022), G051I, G051M, H031F, H131M, H192D, H192J, H220C, H621B
Antiviral treatment in general practice	
Acyclovir	ATC code: J05AB01; Zoster-specific doses identified by Nordic article numbers 005404, 007109, 044597, 057554, 078015, 082158, 106864, 397653, 434183, 447144, 470021, 480533, 496455, 515258, 516328, and 560359
Valacyclovir	ATC code: J05AB011; Zoster-specific doses identified by excluding prescriptions with Nordic article number 030449, 172940, 447695, 498063, or 534343
Famciclovir	ATC code: J05AB09; Zoster-specific doses identified by Nordic article numbers 088196, 455584, 494756, and 550906
Hospital diagnoses of post-herpetic neuralgia	ICD-8: no code available; ICD-10: G530, B022
The UK	
Hospital diagnoses of herpes zoster	ICD-10: B02 (except B022)
Herpes zoster in general practice	Medical codes: 390, 516, 7331, 8936, 14718, 14793, 18918, 21069, 21471, 25320, 27403, 27546, 31681, 33810, 38531, 39692, 43235, 44944, 47375, 50537, 51692, 52126, 52319, 55940, 57895, 62558, 63739, 69405, 70197, 71464, 105157
Hospital diagnoses of post-herpetic neuralgia	ICD-10: G530, B022
Post-herpetic neuralgia in general practice	Medical codes: 1598, 7584, 10223, 11498, 17180, 31709

Abbreviations: ATC = Anatomical Therapeutic Chemical; ICD = International Classification of Diseases

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Supplementary Appendix 3. Additional results, including subgroup and sensitivity analyses

Additional results showing the distribution of herpes zoster risk factors and lifestyle factors among cases and controls is presented in Table 3a below.

In the main analysis, we stratified the results for the 30-day period prior to index date. The results are shown in detail in Table 3b. As we hypothesized that an effect of the immune function could potentially be delayed, we also performed a sensitivity analysis using a 90-day exposure window. The results of this analysis supported the main conclusion, as shown in Table 3c.

We performed analyses including only persons with partners in the reference group. In total, 323,301 (33.9%) and 336,417 (46.3%) participants had no partner in the Danish and British data, respectively. Exclusion of these persons from the reference group did not affect the estimates materially (Table 3d).

We additionally adjusted for the individual-level measures of socioeconomic status, using highest achieved education in Denmark and quintiles of Index of Multiple Deprivation score in the UK. Socioeconomic status was evenly distributed among cases and controls (Table 3e) and adjustment for these measures had no substantial effect on the results (Table 3f).

Smoking and alcohol has been associated with suppression of the immune system and could thus potentially increase the risk of herpes zoster [1,2]. Furthermore, these health-related behaviours are associated with increased risk of death from many causes and could potentially be shared by partners. We therefore examined the impact of adjusting for smoking status, alcohol consumption and obesity in the British data. As 12% had missing data on at least one of these variables, we performed analyses using both complete-case analysis and multiple imputation. Missing data were more frequent among males, in the upper age categories, among patients without the included risk factors for herpes zoster, and among controls. For multiple imputation, we assumed that incomplete data were missing at random and used the method of chained equations to create 20 imputed datasets [3]. We used multinomial models for the imputation procedure and included as predictors the

outcome (case status), age, sex, and all variables from the main outcome model, as well as other lifestyle related diseases, including myocardial infarction, other ischemic heart disease, congestive heart failure, hypertension, cerebrovascular disease, peripheral artery disease, alcoholic liver disease (including portal hypertension) and pancreatitis. We included no non-normally distributed continuous variables. We evaluated the distributions of observed and imputed values for comparability and found them to be consistent. Adjustment for lifestyle factors did not change the results, regardless of the analytical method used to account for missing data (Table 3g).

Because we were concerned about inclusion of other herpes infections in the prescription-based definition in the Danish data, we examined the robustness of our algorithm in a sensitivity analysis excluding cases identified through prescriptions where the indication code did not explicitly state herpes zoster. As indications are recorded since April 2004, this analysis also ensured 10 years of prescription data for ascertaining true first-time prescriptions for antiviral drugs. The indication codes were included only in the sensitivity analysis because of problems with incomplete data (23% included from April 2004 and onwards had no indication recorded) and unspecific coding (e.g., "herpes infection"), and because the validity of indication codes for research has not been examined. The results of this sensitivity analysis were similar to the main analysis (Table 3h).

Table 3a. Characteristics of herpes zoster cases and matched controls. Values are numbers (%)

	Denmark		The UK	
	Cases (n=190,671)	Controls (n=762,684)	Cases (n=150,207)	Controls (n=576,878)
Herpes zoster risk factors[a]				
Rheumatoid arthritis	4,091 (2.1)	9,157 (1.2)	3,904 (2.6)	9,970 (1.7)
Systemic/subacute lupus erythematosus	464 (0.2)	664 (0.1)	454 (0.3)	1,024 (0.2)
Inflammatory bowel disease	2,710 (1.4)	7,324 (1.0)	2,176 (1.4)	6,316 (1.1)
Chronic obstructive pulmonary disease	10,966 (5.8)	31,252 (4.1)	9,473 (6.3)	28,325 (4.9)
Asthma	2,875 (1.5)	8,019 (1.1)	11,214 (7.5)	35,654 (6.2)
Chronic kidney disease	2,826 (1.5)	6,235 (0.8)	11,099 (7.4)	37,370 (6.5)
Diabetes	18,827 (9.9)	68,492 (9.0)	14,486 (9.6)	53,016 (9.2)
Type I	383 (0.2)	1,336 (0.2)	276 (0.2)	873 (0.2)
Type II	17,144 (9.0)	62,647 (8.2)	13,509 (9.0)	49,930 (8.7)
Unknown	1,300 (0.7)	4,509 (0.6)	701 (0.5)	2,213 (0.4)
Inhaled glucocorticoids	11,255 (5.9)	31,515 (4.1)	12,879 (8.6)	38,911 (6.7)
Solid organ transplantation	195 (0.1)	158 (0.02)	247 (0.2)	318 (0.06)
HIV infection	361 (0.2)	364 (0.04)	126 (0.08)	147 (0.03)
Leukemia	782 (0.4)	807 (0.1)	369 (0.2)	558 (0.1)
Lymphoma	1,222 (0.6)	1,034 (0.1)	700 (0.5)	778 (0.1)
Myeloma	486 (0.3)	327 (0.04)	286 (0.2)	254 (0.04)
Stem cell/bone marrow transplantation	692 (0.4)	486 (0.1)	220 (0.1)	114 (0.02)
Other unspecified cellular immune deficiencies	283 (0.1)	382 (0.1)	315 (0.2)	636 (0.1)
Oral glucocorticoids	8,881 (4.7)	16,247 (2.1)	7,397 (4.9)	16,043 (2.8)
Other immunosuppressive treatment	4,309 (2.3)	6,482 (0.8)	3,035 (2.0)	5,589 (1.0)
Lifestyle factors				
Body mass index category				
Underweight	–	–	2,696 (1.8)	10,186 (1.8)
Normal weight	–	–	50,696 (33.8)	192,086 (33.3)
Overweight	–	–	53,145 (35.4)	199,973 (34.7)
Obese	–	–	33,667 (22.4)	126,021 (21.8)
Missing	–	–	10,003 (6.6)	48,612 (8.4)
Smoking status				
Non-smoker	–	–	55,570 (37.0)	215,386 (37.3)
Current smoker	–	–	32,768 (21.8)	132,857 (23.0)
Ex-smoker	–	–	60,844 (40.5)	219,653 (38.1)
Missing	–	–	1,025 (0.7)	8,982 (1.6)
Alcohol use				
Non-drinker	–	–	14,936 (9.9)	58,753 (10.2)
Current drinker	–	–	109,461 (72.9)	413,351 (71.7)
Ex-drinker	–	–	15,331 (10.2)	55,662 (9.6)
Missing	–	–	10,479 (7.0)	49,112 (8.5)

[a] Defined at any time prior to index date, except for leukemia, lymphoma and myeloma (any diagnosis within prior two years) and inhaled glucocorticoids, oral glucocorticoids, and other immunosuppressive treatment (any record within prior 90 days).

Table 3b. Odds ratios for the association between partner bereavement within previous 30 days and herpes zoster, subgroup analysis

	Denmark				The UK			
	Cases, number (%)	**Controls, number (%)**	**Unadjusted odds ratio (99% CI)**	**Adjusted odds ratio (99% CI)[a]**	**Cases, number (%)**	**Controls, number (%)**	**Unadjusted odds ratio (99% CI)**	**Adjusted odds ratio (99% CI)[a]**
Partner's risk of death[b]								
Low	17 (0.01)	107 (0.01)	0.64 (0.33 to 1.26)	0.64 (0.32 to 1.26)	11 (0.01)	39 (0.01)	1.13 (0.47 to 2.72)	1.16 (0.48 to 2.80)
Intermediate	65 (0.03)	294 (0.04)	0.90 (0.63 to 1.28)	0.92 (0.65 to 1.32)	34 (0.02)	122 (0.02)	1.08 (0.66 to 1.79)	1.11 (0.67 to 1.83)
High	65 (0.03)	251 (0.03)	1.05 (0.73 to 1.51)	1.06 (0.74 to 1.52)	36 (0.02)	155 (0.03)	0.91 (0.57 to 1.47)	0.91 (0.57 to 1.48)
Partner terminal								
No	–	–	–	–	65 (0.04)	227 (0.04)	1.12 (0.78 to 1.61)	1.13 (0.79 to 1.63)
Yes	–	–	–	–	16 (0.01)	89 (0.02)	0.71 (0.35 to 1.43)	0.72 (0.36 to 1.46)
Sex								
Female	112 (0.06)	436 (0.06)	1.13 (0.86 to 1.49)	1.14 (0.87 to 1.51)	54 (0.04)	208 (0.04)	1.02 (0.69 to 1.52)	1.03 (0.69 to 1.53)
Male	35 (0.02)	216 (0.03)	0.56 (0.35 to 0.90)	0.57 (0.36 to 0.92)	27 (0.02)	108 (0.02)	0.97 (0.56 to 1.70)	0.99 (0.57 to 1.73)
Age at index date (years)								
40–49	5 (0.003)	14 (0.002)	1.44 (0.38 to 5.54)	1.45 (0.38 to 5.56)	1 (0.0006)	5 (0.0009)	0.80 (0.05 to 13.51)	0.86 (0.05 to 14.50)
50–59	13 (0.01)	70 (0.01)	0.75 (0.34 to 1.63)	0.70 (0.32 to 1.55)	6 (0.003)	20 (0.003)	1.15 (0.35 to 3.82)	1.13 (0.34 to 3.80)
60–69	29 (0.02)	138 (0.02)	0.85 (0.50 to 1.44)	0.84 (0.49 to 1.43)	16 (0.01)	62 (0.01)	1.02 (0.50 to 2.11)	1.01 (0.49 to 2.09)
≥70	100 (0.05)	430 (0.06)	0.94 (0.71 to 1.25)	0.97 (0.73 to 1.29)	58 (0.04)	229 (0.04)	0.99 (0.68 to 1.45)	1.01 (0.69 to 1.48)
Recent depression/anxiety								
No	129 (0.07)	580 (0.08)	0.92 (0.72 to 1.19)	0.93 (0.72 to 1.20)	80 (0.05)	310 (0.05)	1.01 (0.73 to 1.40)	1.01 (0.74 to 1.42)
Yes	18 (0.01)	72 (0.01)	0.82 (0.42 to 1.62)	0.85 (0.43 to 1.69)	1 (0.0006)	6 (0.001)	0.58 (0.04 to 9.37)	0.57 (0.04 to 9.38)

[a]Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs and inhaled glucocorticoids.

[b]Measured by the age-adjusted Charlson Comorbidity Index with the total score categorized as low (0–3 points), intermediate (4–6 points) or high (≥7 points).

Table 3c. Odds ratios for the association between partner bereavement within previous 90 days and herpes zoster, subgroup analysis

	Denmark				The UK			
	Cases, number (%)	Controls, number (%)	Unadjusted odds ratio (99% CI)	Adjusted odds ratio (99% CI)[a]	Cases, number (%)	Controls, number (%)	Unadjusted odds ratio (99% CI)	Adjusted odds ratio (99% CI)[a]
Partner's risk of death[b]								
Low	59 (0.03)	298 (0.04)	0.80 (0.55 to 1.15)	0.79 (0.55 to 1.14)	26 (0.02)	122 (0.02)	0.84 (0.48 to 1.47)	0.82 (0.47 to 1.44)
Intermediate	233 (0.12)	871 (0.11)	1.09 (0.90 to 1.32)	1.10 (0.91 to 1.34)	112 (0.07)	374 (0.06)	1.16 (0.88 to 1.53)	1.18 (0.89 to 1.57)
High	198 (0.10)	756 (0.10)	1.07 (0.87 to 1.31)	1.07 (0.87 to 1.32)	114 (0.08)	449 (0.08)	0.99 (0.76 to 1.30)	0.99 (0.75 to 1.30)
Partner terminal								
No	–	–	–	–	187 (0.12)	711 (0.12)	1.02 (0.83 to 1.26)	1.02 (0.82 to 1.26)
Yes	–	–	–	–	65 (0.04)	234 (0.04)	1.09 (0.76 to 1.57)	1.11 (0.77 to 1.60)
Sex								
Female	366 (0.19)	13,11 (0.17)	1.24 (1.06 to 1.44)	1.25 (1.07 to 1.46)	183 (0.12)	638 (0.11)	1.13 (0.91 to 1.40)	1.13 (0.91 to 1.40)
Male	124 (0.07)	614 (0.08)	0.70 (0.54 to 0.90)	0.70 (0.54 to 0.91)	69 (0.05)	307 (0.05)	0.86 (0.61 to 1.21)	0.86 (0.61 to 1.22)
Age at index date (years)								
40–49	18 (0.01)	44 (0.01)	1.65 (0.80 to 3.40)	1.65 (0.80 to 3.41)	2 (0.001)	14 (0.002)	0.54 (0.08 to 3.82)	0.58 (0.08 to 4.10)
50–59	37 (0.02)	189 (0.02)	0.79 (0.50 to 1.26)	0.76 (0.47 to 1.21)	16 (0.01)	71 (0.01)	0.86 (0.42 to 1.75)	0.84 (0.41 to 1.71)
60–69	112 (0.06)	402 (0.05)	1.12 (0.85 to 1.48)	1.11 (0.84 to 1.47)	49 (0.03)	172 (0.03)	1.12 (0.73 to 1.70)	1.10 (0.72 to 1.68)
≥70	323 (0.17)	1,290 (0.17)	1.01 (0.86 to 1.19)	1.03 (0.88 to 1.22)	185 (0.12)	688 (0.12)	1.05 (0.85 to 1.30)	1.06 (0.85 to 1.31)
Recent depression/anxiety								
No	422 (0.22)	1,726 (0.23)	1.01 (0.88 to 1.17)	1.02 (0.89 to 1.18)	247 (0.16)	909 (0.16)	1.06 (0.88 to 1.28)	1.06 (0.88 to 1.28)
Yes	68 (0.04)	199 (0.03)	1.12 (0.78 to 1.61)	1.15 (0.80 to 1.66)	5 (0.003)	36 (0.01)	0.48 (0.14 to 1.64)	0.48 (0.14 to 1.64)

[a]Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs and inhaled glucocorticoids.

[b]Measured by the age-adjusted Charlson Comorbidity Index with the total score categorized as low (0–3 points), intermediate (4–6 points) or high (≥7 points).

Table 3d. Odds ratios (99% confidence intervals) for the association between partner bereavement and herpes zoster. Sensitivity analysis including only persons with partners in the reference group

	Denmark		The UK	
	Unadjusted odds ratio	**Adjusted odds ratio[a]**	**Unadjusted odds ratio**	**Adjusted odds ratio[a]**
Never bereaved	(reference)	(reference)	(reference)	(reference)
Bereaved	1.06 (1.04 to 1.09)	1.06 (1.04 to 1.08)	0.99 (0.96 to 1.03)	0.99 (0.95 to 1.02)
0–7 days	0.67 (0.39 to 1.15)	0.67 (0.39 to 1.16)	0.79 (0.39 to 1.61)	0.80 (0.39 to 1.63)
8–14 days	1.01 (0.60 to 1.69)	1.03 (0.61 to 1.74)	0.68 (0.31 to 1.47)	0.67 (0.31 to 1.46)
15–30 days	1.00 (0.74 to 1.36)	1.01 (0.74 to 1.37)	1.21 (0.80 to 1.83)	1.23 (0.82 to 1.86)
31–90 days	1.10 (0.94 to 1.29)	1.11 (0.94 to 1.30)	1.04 (0.83 to 1.29)	1.03 (0.82 to 1.29)
91–365 days	1.08 (1.00 to 1.16)	1.08 (1.00 to 1.16)	0.96 (0.87 to 1.07)	0.96 (0.86 to 1.07)
366–1095 days	1.07 (1.02 to 1.12)	1.06 (1.01 to 1.12)	1.00 (0.93 to 1.07)	0.99 (0.93 to 1.07)
>1095 days	1.06 (1.04 to 1.09)	1.06 (1.03 to 1.08)	0.99 (0.95 to 1.04)	0.99 (0.95 to 1.03)

[a]Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs and inhaled glucocorticoids.

Table 3e. Measures of patient-level socioeconomic status among cases and matched controls

	Cases n (%)	Controls n (%)
Denmark		
Highest achieved education		
Long (>15 years)	33,006 (17.3)	121,098 (15.9)
Medium (>10–15 years)	72,508 (38.0)	295,076 (38.7)
Short (≤10 years)	66,494 (34.9)	269,752 (35.4)
Missing	18,663 (9.8)	76,758 (10.1)
The UK		
Quintile of Index of Multiple Deprivation score		
1 (least deprived)	23,452 (15.6)	90,245 (15.6)
2	23,400 (15.6)	89,782 (15.6)
3	19,261 (12.8)	74,420 (12.9)
4	15,471 (10.3)	59,239 (10.3)
5 (most deprived)	11,107 (7.4)	42,102 (7.3)
Missing	57,516 (38.3)	221,090 (38.3)

Table 3f. Odds ratios (99% confidence intervals) for the association between partner bereavement and herpes zoster, adjusting for risk factors for herpes zoster and socioeconomic status[a]

	Denmark	The UK
Never bereaved	(reference)	(reference)
Bereaved	1.06 (1.04 to 1.08)	1.00 (0.95 to 1.04)
0–7 days	0.77 (0.44 to 1.36)	0.43 (0.13 to 1.45)
8–14 days	1.14 (0.65 to 1.99)	0.75 (0.29 to 1.94)
15–30 days	1.05 (0.76 to 1.45)	1.28 (0.77 to 2.12)
31–90 days	1.10 (0.92 to 1.31)	1.05 (0.79 to 1.38)
91–365 days	1.11 (1.02 to 1.20)	0.93 (0.81 to 1.07)
366–1095 days	1.09 (1.03 to 1.15)	1.01 (0.93 to 1.11)
>1095 days	1.05 (1.03 to 1.08)	1.00 (0.95 to 1.05)

[a]Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, inhaled glucocorticoids and patient level socioeconomic status (quintiles of the Index of Multiple Deprivation Score in the UK and highest achieved education in Denmark)

Table 3g. Odds ratios (99% confidence intervals) for the association between partner bereavement and herpes zoster, adjusting for risk factors for herpes zoster and lifestyle factors in the British data[a]

	Complete-case analysis	Multiple imputation
Never bereaved	(reference)	(reference)
Bereaved	1.01 (0.97 to 1.04)	1.01 (0.98 to 1.05)
0–7 days	0.81 (0.38 to 1.76)	0.82 (0.40 to 1.68)
8–14 days	0.58 (0.24 to 1.40)	0.69 (0.32 to 1.50)
15–30 days	1.28 (0.82 to 1.99)	1.27 (0.84 to 1.92)
31–90 days	1.03 (0.81 to 1.31)	1.05 (0.84 to 1.32)
91–365 days	1.01 (0.90 to 1.13)	0.98 (0.89 to 1.10)
366–1095 days	1.02 (0.94 to 1.10)	1.02 (0.95 to 1.09)
>1095 days	1.00 (0.96 to 1.05)	1.01 (0.97 to 1.06)

[a]Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, inhaled glucocorticoids, body mass index category, smoking status and alcohol use.

Table 3h. Adjusted odds ratios (99% confidence intervals)[a] for the association between partner bereavement and herpes zoster. Sensitivity analyses examining the robustness of the prescription-based definition of herpes zoster in the Danish data

	Main analysis (entire study population)	**Excluding those with indication codes not explicitly stating herpes zoster**
Never bereaved	(reference)	(reference)
Bereaved	1.05 (1.03 to 1.07)	1.04 (1.01-1.08)
0–7 days	0.67 (0.38 to 1.15)	0.70 (0.31-1.58)
8–14 days	1.03 (0.61 to 1.73)	1.13 (0.54-2.35)
15–30 days	1.01 (0.74 to 1.37)	0.98 (0.61-1.60)
31–90 days	1.10 (0.94 to 1.29)	1.07 (0.83-1.38)
91–365 days	1.07 (0.99 to 1.15)	1.08 (0.96-1.21)
366–1095 days	1.06 (1.01 to 1.11)	1.07 (0.99-1.15)
>1095 days	1.05 (1.03 to 1.07)	1.04 (1.01-1.07)

[a]Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs and inhaled glucocorticoids.

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Supplementary appendices 4 and 5

Supplementary appendices 4 and 5, which provide the study protocols with complete code lists, are available at *Clinical Infectious Diseases* online.

Paper III

- **Appendix III**:

Mood disorders and risk of herpes zoster in two population-based case-control studies in Denmark and the United Kingdom

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Abbreviations:

aOR = adjusted odds ratio

CI = confidence interval

CMI = cell-mediated immunity

CPRD = Clinical Practice Research Datalink

HES = Hospital Episodes Statistics database

ICD = International Classification of Diseases

UK = United Kingdom

VZV = varicella zoster virus

Contributors: All authors participated in designing the study. HSP performed sampling and initial data management of the Danish data. SAJS performed remaining analyses. All authors participated in the discussion and interpretation of the results. SAJS wrote the initial manuscript draft. All authors critically revised the manuscript for intellectual content and approved the final version. SAJS is the guarantor.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the UK Department of Health.

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Ethics: The Danish study was approved by the Danish Data Protection Agency (2013-41-1719). Danish legislation does not require approval by an ethical review board or informed consent from patients for registry-based studies. The British study was approved by the CPRD Independent Scientific Advisory Committee (15_248) and the London School of Hygiene and Tropical Medicine Ethics Committee (11219). Study protocols, including complete variable definitions and code lists, are available from the corresponding author upon request.

ABSTRACT

Cell-mediated immunity against varicella zoster virus is reduced in depressed people, possibly increasing their risk of herpes zoster. We examined this hypothesis in two case-control studies using data from nationwide Danish registries and practices in the UK Clinical Practice Research Datalink. We included cases of incident zoster diagnosed in general practice (using systemic antivirals as proxy in Denmark) or hospital during 1997–2013 in Denmark (n=190,671) and during 2000–2013 in the UK (n=177,361). We risk-set sampled four matched population controls for each case. Conditional logistic regression analyses showed that the adjusted odds ratios (aORs) for previous mood disorder among cases *vs.* controls were 1.15 (99% confidence interval (CI): 1.12, 1.19) in Denmark and 1.12 (99% CI: 1.11, 1.14) in the UK. In Denmark, aORs were higher for anxiety (1.23; 99% CI: 1.17, 1.30) and severe stress and adjustment disorder (1.24; 99% CI: 1.18, 1.30) than for depression (1.11; 99% CI: 1.07, 1.14). In the UK, aORs for these conditions were similar: 1.12 (99% CI: 1.10, 1.13), 1.12 (99% CI: 1.10, 1.14), and 1.14 (99% CI: 1.10, 1.19) for depression, anxiety, and severe stress and adjustment disorder, respectively. In conclusion, mood disorders were associated with an increased risk of zoster.

Keywords: adjustment disorders; anxiety; depression; herpes zoster; stress disorders

Herpes zoster is caused by reactivation of the varicella-zoster virus (VZV) from sensory ganglia when cellular immunity wanes below a critical level (1). Mood disorders, such as depression and anxiety, have been associated with impaired cell-mediated immunity (CMI) (2). In particular, it has been demonstrated that VZV-specific CMI is reduced in major depression (3,4) and is negatively associated with severity (3). Nevertheless, there are few well-designed epidemiological studies estimating the risk of zoster in persons with mood disorders.

Registry-based case-control and cohort studies using prospectively-collected data have found relative risks of zoster ranging between 1.11 and 1.52 for persons with depression compared with those without depression (5-10); studies using self-reported data on depression found relative risks between 0.93 and 4.15 (11-14). Unfortunately, these studies were hampered by methodological limitations, such as use of broad exposure definitions (e.g., mixing depression with alcohol-related psychotic disorder) (7-9), potential reverse causation (13,14), selection bias (8,9,13,14), and over-adjustment by including possible proxies for exposure (9,10). Furthermore, no studies have evaluated whether associations depend on time since diagnosis and severity of mood disorders.

We therefore aimed to quantify the risk of zoster among persons with a range of mood disorders, including depression, anxiety, and severe stress and adjustment disorder, taking into account time since diagnosis and severity of these disorders.

METHODS

Data sources

We created two case-control datasets using population-based registries in Denmark and the UK. The study period was January 1, 1997–December 31, 2013 in Denmark and in January 1, 2000–December 31, 2013 in the UK.

In Denmark, we retrieved nationwide data on hospital diagnoses from the National Patient Registry (15) and the Psychiatric Central Registry (16). These registries provided data on inpatient psychiatric contacts since 1970, inpatient non-psychiatric contacts since 1978, and outpatient specialty clinic and emergency department visits since 1995 (15,16). For each encounter, a primary diagnosis (the main reason for contact) and optional secondary diagnoses are recorded using the *International Classification of Diseases, Eighth Revision* (ICD-8) until the end of 1993 and *Tenth Revision* (ICD-10) thereafter. We also obtained hospital data on surgical procedures and specialized treatments (*e.g.*, delivery of chemotherapy). The Danish National Prescription Registry was used to identify prescriptions dispensed at any community pharmacy since 1995 (including date of dispensing, Anatomical Therapeutic Chemical code for the drug, and number and strength of tablets/units)(17). We ascertained diagnoses of diabetes (as a covariate) using the Danish National Diabetes Registry, which identifies diabetics based on hospital-based diabetes diagnoses, reimbursable chiropody, blood-glucose measurements, and prescriptions for diabetes drugs (18). The Danish Population Education Registry provided information on the highest level of education attained by study participants as a proxy for socioeconomic status (19). We linked the Danish registries using the unique personal identifier assigned to all residents by the Civil Registration System (20).

In the UK, we used the Clinical Practice Research Datalink (CPRD) (21), the Hospital Episodes Statistics (HES) database (22) and the Index of Multiple Deprivation (23). The CPRD contains primary healthcare data for 11.3 million patients from 674 general practices in the UK (21). Practices collect data on reasons for patient contacts (using Read codes), written prescriptions (using the Multilex Product Dictionary), vaccinations, laboratory and clinical measurements, lifestyle factors, anthropometric data, and referrals to secondary care (21). Internal practice- and patient-level quality checks identifies data adequate for research.

Approximately 60% of practices allow linkage to other datasets. We obtained inpatient hospital data from HES, in which primary and secondary diagnoses are recorded according to the ICD-10 system and procedures according to the Office of Population and Censuses and Surveys Classification of Interventions and Procedures, version 4 (22). The Index of Multiple Deprivation (2010 version) provided data on individual-level and practice-level deprivation. The Index weights 38 indicators within various domains, such as income and education (23), to yield deprivation scores for small geographical areas, which are mapped to practice or home postcode.

Cases

Diagnoses of zoster from primary care are not reported to the Danish registries. We therefore identified zoster cases by prescriptions recorded in the National Prescription Registry for systemic antivirals at doses most compatible with zoster treatment (35 tablets of 800 mg acyclovir, or packets with 500-mg tablets of valacyclovir or famciclovir)(24). As these agents also are used for severe primary and reactivated herpes simplex infections (25), which occur most commonly in young people (26), persons eligible for the study had to be aged ≥40 years when dispensing their first-time prescription for one of the antivirals. We retrieved hospital diagnoses of zoster from the Danish National Patient Registry, restricted to patients aged ≥40 years for consistence. We aimed to capture only incident zoster by excluding cases with previous records potentially representing chronic complication from zoster (defined as post-herpetic neuralgia or any previous secondary zoster hospital diagnosis). The index date for cases was the date of prescription, hospital admission or start of outpatient follow-up, whichever came first for persons with multiple records.

In the UK, cases were those with a record of zoster in the CPRD or a hospital diagnosis in HES, and no previous record of chronic complications from zoster (defined as above). The

index date was the first occurring consultation or admission date for zoster. To avoid including prevalent zoster recorded shortly after registration with a new practice, cases had to have ≥12 months of registration with their current practice (27).

Controls

We used risk-set sampling (28) from the Civil Registration System in Denmark and the CPRD in the UK to match up to four controls to each case by age, sex, and general practice (UK only). Controls received an index date identical to their case. We applied the same eligibility criteria to controls as for cases. In the UK, we excluded matched controls who had no contact with their CPRD practice within the 6 months before and 12 months after the index date, as they were considered inactive (5).

Mood Disorder

We identified all records of depression, anxiety, and severe stress and adjustment disorder before the index zoster diagnosis in the Danish hospital registries and in the UK CPRD or HES. To accommodate trends in coding of depression in UK primary care (29), we included Read codes in the CPRD both for diagnoses and symptoms of depression. We categorized mood disorder in subgroups of timing and severity (Table 1), to examine our hypothesis that persons with current ('active') and severe mood disorders have a higher risk of zoster. Of note, 'mild severity' may be least comparable between countries, as persons treated for a mood disorder in general practice alone were not included in the Danish data.

Statistical analysis

We used conditional logistic regression to compute unadjusted odds ratios (ORs) with 99% confidence intervals (CIs), associating zoster with history of the three mood disorders

separately and combined. Given the risk-set matching, the ORs provide unbiased estimates of incidence rate ratios (28). In multivariable analyses, we additionally adjusted for zoster risk factors (5) listed in Table 2. We stratified results for current mood disorders by age and sex. Finally, to assess the public health relevance, we computed the absolute age-specific rate of zoster for persons with any previous mood disorder diagnosis by multiplying the age-specific effect estimates in the Danish and UK study populations by the age-specific rate of zoster in the CPRD population in 2010 (5).

Additional analyses

Web Appendix 1 provides a detailed account of additional analyses. In a subgroup analysis, we examined whether ORs of zoster for current mood disorders were more pronounced for persons with their first-ever record of a mood disorder (*i.e.*, 'new-onset' conditions) within the 90 days before the index date (zoster diagnosis date for cases and their matched controls). We also conducted various sensitivity analyses. We included data on antidepressant prescriptions to: (i) capture mood disorders treated in Danish general practice and (ii) examined the following alternative definition of severity: very severe ('severe' group in main analysis), severe ('moderate' group in main analysis), moderate (antidepressant prescription within the past 90 days); or mild (remaining patients). We disregarded prescriptions redeemed in the two weeks before the index date to exclude treatment of zoster-associated pain. Second, we changed the defining cut-off for current mood disorder to within 7, 14, 30, and 180 days of the index date. Third, we excluded persons with only possible/unspecific codes for mood disorder (*e.g.*, 'suspected depression'). Fourth, we excluded persons with more than one type of mood disorder. Fifth, we excluded Danish cases identified by antiviral prescriptions without a zoster indication code (codes were considered too incomplete for use in the main analyses). Sixth, we excluded case-control sets included after marketing of the

zoster vaccine on 31 August 2013 in the UK (not available in Denmark during study). Finally, we additionally adjusted for: (i) individual-level socioeconomic status (highest achieved education in Denmark and Index of Multiple Deprivation score in the UK) and (ii) smoking status, alcohol consumption, and body mass index (UK only).

Against our expectations, we found the lowest ORs for severe mood disorders. To examine if this lack of association could be explained by underascertainment of zoster diagnosed during hospital follow-up of patients recently admitted with mood disorder, we performed a *post-hoc* analysis where we included secondary hospital diagnoses of zoster in the case definitions.

RESULTS

The study included 190,671 cases (people with incident zoster) and 762,684 controls (without incident zoster) in Denmark, and 177,361 cases and 674,503 controls in the UK (Web Appendix 2, Figure e1). Although the prevalence of some covariates differed between Denmark and the UK, the relative differences between cases and controls were similar (Table 2).

Cases had a higher recorded lifetime prevalence of mood disorder than controls (7.1% *vs.* 6.0% in Denmark; 31.6% *vs.* 29.2% in the UK), with depression being the most frequent mood disorder (Table 3). Adjustment for risk factors had little effect on ORs (Web Appendix 2, Tables e1 and e2). The adjusted ORs (aOR) for history of mood disorder among zoster cases compared with controls was 1.15 (99% CI: 1.12, 1.19) in Denmark and 1.12 (99% CI: 1.11, 1.14) in the UK (Table 3). In Denmark, we observed slightly higher aORs for anxiety (1.23; 99% CI: 1.17, 1.30) and severe stress and adjustment disorder (1.24; 99% CI 1.18, 1.30) than for depression (1.11; 99% CI: 1.07, 1.14). In the UK, estimates were similar for the three disorders. No substantial difference was observed when considering current, recent,

or former mood disorders separately, although slightly higher aORs were observed for current and recent diagnoses than for former diagnoses in the UK (Table 3). Analyses according to severity found that the overall increased risk of zoster was restricted to those with mild and moderate mood disorders, but confidence intervals were wide (Table 4).

In analyses by sex, the aOR for current mood disorder among zoster cases compared with controls were increased only among women (Table 5). Furthermore, the aORs decreased with increasing age in the UK (Table 5), which seemed explained by the results for depression (Table e3). The differences in absolute rates between persons with any previous mood disorder and the general population was 0.46–0.63 per 1,000 person-years in Denmark and 0.63–0.92 per 1,000 person-years in the UK, without variation by age (Table 6).

Additional analyses

Estimates were not more pronounced for those with first-time diagnosis in the current exposure period (Table e1). When including antidepressant prescriptions as proxy for mood disorder in Denmark, lifetime prevalence approached that in the UK study (27.0% of cases and 22.2% of controls) and the aOR for any previous mood disorder increased to 1.26 (99% CI: 1.24–1.28) (Table e5). The increase was observed across subgroups defined by timing and severity, but remained lowest for patients with a recent hospitalization (1.11, 99% CI: 0.91, 1.34). Results were robust in remaining sensitivity analyses (Tables e6–e12).

In *post-hoc* analyses including secondary hospital diagnoses of zoster in the case definitions (Tables e13–e15), we identified 576 and 1,137 additional zoster cases in Denmark and the UK. In Denmark, the aOR for inpatient admission due to mood disorder increased to 1.12 (99% CI: 0.93, 1.35) and to 1.19 (99% CI: 0.98, 1.43) when excluding antidepressant users from the reference group. The estimates for current mood disorder remained low for men, but decreased with increasing age, as observed in the UK main analyses. In the UK, the

aOR for severe mood disorders increased to 1.16 (99% CI: 0.94, 1.43). Furthermore, aORs for current mood disorder became similar for men (1.25; 99% CI: 1.13, 1.37) and women (1.29; 99% CI: 1.22, 1.36).

DISCUSSION

In two large population-based studies from Denmark and the UK, we found that several mood disorders are associated with increased relative risk of zoster. The risk was increased even for those with more than one year since last healthcare contact for mood disorder and among those classified as having mild disease.

Previous registry-based studies from Europe (5,6), the United States (7) and East Asia (8-10) have reported 11%–52% increases in relative risk of zoster among persons with depression. Although most studies thus support an association between mood disorders and zoster of similar magnitude to that found in our study, direct comparison with existing evidence is hampered by previous studies using broad definitions of depression (7-9), which included bipolar disorder, depressive personality disorder, and late psychotic disorder due to alcoholic use. Furthermore, one cohort study adjusted for antidepressant use within six months before the endpoint (10). Finally, two cohort studies selected comparison cohorts based on factors that may be predict zoster (*e.g.*, diagnosis of cancer (8) or absence of psychiatric diagnosis during follow-up (9)).

Four other studies used self-reported data on mood disorders (11-14). The hazard ratios of zoster were not increased among depressed persons in two cohort studies from the US (0.93 [95% CI: 0.51, 1.71]) (11) and Australia (1.01 [95% CI: 0.95, 1.08]) (12). However, the Australian study adjusted for self-rated health, which may be related to depression, thus inevitably leading to over-adjustment (1,11,19). Two smaller studies found associations between zoster and symptoms of depression (ORs 2.00–4.15) (13,14), but not anxiety (OR

1.07) (13). Besides potential selection bias in these studies, symptoms of mood disorder were assessed up to 3 weeks after rash onset. This design may have led to recall bias and reverse causation (13,14), as neuralgia associated with zoster may impact mental health (30).

The mechanisms underlying an association between mood disorders and zoster are unknown. Decreased VZV-CMI has been found in patients with major depression compared with age- and sex-matched non-depressed controls (3,4). Furthermore, the Depression Substudy of the Shingles Prevention Study showed that boosting of VZV-CMI following zoster vaccination was lower in the untreated depressed group compared with persons treated with antidepressants and non-depressed persons (4). Although this immunosuppression in mood disorder may result from persistent activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system during chronic stress (2), the death or acute illness of a partner, as a measure of extreme stress, was not associated with zoster in two studies (31,32). As bereavement and mood disorders are distinct psychological states, we hypothesize that these contradictory findings are explained by a greater allostatic load in the latter (2). Indeed, reductions in immune function following negative life events correlate with presence and severity of depressive symptoms (33,34). The increased ORs for former mood disorders supports that such alterations in immune function are prolonged, or alternatively that shared biological or personal factors, *e.g.*, a genetic susceptibility to both mood disorders and zoster, may play a role.

With almost 70,000 exposed cases of zoster, our study is by far the largest on the topic. Additional strengths include use of population-based prospective data and adjustment for various zoster risk factors. A concern is that while Denmark has comprehensive hospital registries covering psychiatric and non-psychiatric inpatient units and specialized outpatient clinics, we had to use prescription data as proxies for diagnoses from Danish primary care. Conversely, we had comprehensive general practice data from the UK, but hospital data were

limited to admissions and only available for 60% of participants. Because of these methodological differences, we did not pool results in a meta-analysis. Nevertheless, estimates were remarkably similar and the complementary strengths and weaknesses of the two sources of data were advantageous in allowing us to explore different types of bias, *e.g.*, potential confounding from lifestyle factors.

Detection of zoster because of increased medical attendance in patients with mood disorders is a possible threat to the validity in both datasets. On the other hand, avoidance symptoms in post-traumatic stress disorder and social anxiety, or the loss of energy in depression, could preclude care seeking in some patients. Similarly, the lack of an association between mood disorders and zoster among those with severe mood disorder, may be explained by decreased health-seeking. However, the *post-hoc* analyses, including secondary (rather than exclusively primary) zoster hospital diagnoses, suggested that this lack of association may have been due to excluding secondary zoster diagnoses made at psychiatric hospitals subsequent to an admission for a mood disorder.

Delay from true onset of mood disorder to a diagnosis in our data may have affected analyses focusing on timing, if some patients seek care late. Underestimation due to misclassification of persons with mood disorder in the reference group is another potential limitation (29,35-37). This bias is evident from the increase in ORs when we included antidepressants as a proxy for mood disorder in Denmark. The low ORs among men may result from more pronounced non-differential misclassification than in women, as men seek and receive treatment for mood disorders less frequently (38). The lower ORs among elderly may also be explained by underdiagnosis, as somatic presentation is more common in late-life depression (39). Furthermore, it is possible that persons diagnosed with mood disorder at older ages have already experienced zoster for another reason or simply that stronger risk factors play a relatively greater role than mood disorders. Regardless, the absolute increase in

rate associated with any mood disorder supported a potential benefit of zoster prevention at all ages.

In summary, previous studies show that VZV-CMI is reduced in patients with major depression (3,4). Our study extends these immunological findings and understanding of its potential clinical consequences by showing that several mood disorders were associated with an increased risk of zoster.

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Table 1. Exposure Definitions[a]

Main definition	
Never (reference)	No previous healthcare record of mood disorder before the index date
Ever	Any previous healthcare record of mood disorder before the index date
Timing	
Current	Most recent record within ≤90 days before the index date
Recent	Most recent record within >90–365 days before the index date
Former	Most recent record within >365 days before the index date; all codes stating "in remission" were classified in this subgroup
Severity[b]	
Severe	Requiring hospital admission with the condition documented as the primary diagnosis within ≤90 days before the index date
Moderate	Persons with any other hospital contact for the condition (Denmark) or referral from general practice to a mental health service, *e.g.,* a psychologist (the UK) within ≤90 days before the index date
Mild	Remaining patients with record of any mood disorder ever before index date

[a]The index date is the zoster diagnosis or prescription date (in Denmark) for cases and their matched controls.
[b]In the UK, the severity classification was examined only among patients with data linked to the Hospital Episodes Statistics database.

Table 2. Distribution of Matching Factors and Herpes Zoster Risk Factors Among Herpes Zoster Cases and Matched Controls in Denmark (1997–2013) and the United Kingdom (2000–2013). Values are Numbers (Percentages)

	Denmark		UK	
	Cases (n=190,671)	**Controls (n=762,684)**	**Cases (n=177,361)**	**Controls (n=674,503)**
Sex				
Women	125,526 (65.8)	502,104 (65.8)	105,356 (59.4)	411,126 (61.0)
Men	65,145 (34.2)	260,580 (34.2)	72,005 (40.6)	263,377 (39.0)
Age at index date (years)				
18–39			27,154 (15.3)	97,625 (14.5)
40–49	34,838 (18.3)	139,352 (18.3)	20,844 (11.8)	77,009 (11.4)
50–59	41,898 (22.0)	167,592 (22.0)	33,632 (19.0)	127,508 (18.9)
60–69	45,662 (23.9)	182,648 (23.9)	38,437 (21.7)	150,110 (22.3)
70–79	39,264 (20.6)	157,056 (20.6)	34,767 (19.6)	136,694 (20.3)
80–89	23,968 (12.6)	95,872 (12.6)	19,454 (11.0)	755,66 (11.2)
≥90	5,041 (2.6)	20,164 (2.6)	3,073 (1.7)	9,991 (1.5)
Practice-level IMD score (quintiles)*				
1 (least deprived)			34,965 (19.7)	132,980 (19.7)
2			34,942 (19.7)	132,805 (19.7)
3			37,861 (21.3)	144,034 (21.4)
4			36,017 (20.3)	136,752 (20.3)
5 (most deprived)			33,576 (18.9)	127,932 (19.0)
Herpes zoster risk factors†				
Rheumatoid arthritis	4,091 (2.1)	9,157 (1.2)	4,031 (2.3)	10,187 (1.5)
SLE	464 (0.2)	664 (0.1)	525 (0.3)	1,093 (0.2)
IBD	2,710 (1.4)	7,324 (1.0)	2,499 (1.4)	6,879 (1.0)
COPD	10,966 (5.8)	31,252 (4.1)	9,479 (5.3)	28,342 (4.2)
Asthma	2,875 (1.5)	8,019 (1.1)	13,714 (7.7)	42,857 (6.4)
CKD	2,826 (1.5)	6,235 (0.8)	11,196 (6.3)	37,490 (5.6)
Diabetes	18,827 (9.9)	68,492 (9.0)	14,880 (8.4)	54,085 (8.0)
Inhaled glucocorticoids	11,255 (5.9)	31,515 (4.1)	13,987 (7.9)	41,828 (6.2)
Solid organ transplantation	195 (0.1)	158 (0.02)	293 (0.2)	347 (0.05)
HIV infection	361 (0.2)	364 (0.04)	196 (0.1)	206 (0.03)
Leukemia	782 (0.4)	807 (0.1)	392 (0.2)	565 (0.08)
Lymphoma	1,222 (0.6)	1,034 (0.1)	757 (0.4)	799 (0.1)
Myeloma	486 (0.3)	327 (0.04)	291 (0.2)	254 (0.04)
HSCT	692 (0.4)	486 (0.1)	278 (0.2)	138 (0.02)
Other cellular immune deficiency	283 (0.1)	382 (0.1)	345 (0.2)	668 (0.1)
Oral glucocorticoids	8,881 (4.7)	16,247 (2.1)	7,795 (4.4)	16,676 (2.5)
Other immunosuppressants	4,309 (2.3)	6,482 (0.8)	3,313 (1.9)	5,830 (0.9)

Abbreviations: CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; HSCT = hematopoietic stem cell transplantation; IBD = inflammatory bowel disease; IMD = Index of Multiple Deprivation; SLE = subacute/systemic lupus erythematosus

*By matching on general practice in the United Kingdom data.

†Defined at any time prior to index date, except for leukemia, lymphoma and myeloma (any diagnosis within prior two years) and inhaled glucocorticoids, oral glucocorticoids, and other immunosuppressive treatment (any record within prior 90 days). Distributions of variables used in sensitivity analyses (lifestyle factors and measures of socioeconomic status) are shown in Web Appendix 2.

Table 3. Adjusted odds ratios for previous diagnosis of mood disorder among herpes zoster cases compared with matched controls in Denmark (1997–2013) and the United Kingdom (2000–2013), by timing of mood disorder

	Denmark			The United Kingdom		
	Cases (%) / Controls (%)	**OR[a]**	**99% CI**	**Cases (%) / Controls (%)**	**OR[a]**	**99% CI**
Any mood disorder						
Never	177,196 (92.9) / 716,894 (94.0)	(reference)		121,307 (68.4) / 477,608 (70.8)	(reference)	
Ever	13,475 (7.1) / 45,790 (6.0)	1.15	1.12, 1.19	56,054 (31.6) / 196,895 (29.2)	1.12	1.11, 1.14
Current	585 (0.3) / 1,867 (0.2)	1.18	1.04, 1.34	3,778 (2.1) / 12,400 (1.8)	1.18	1.13, 1.24
Recent	1,297 (0.7) / 4,133 (0.5)	1.20	1.10, 1.31	7,615 (4.3) / 24,751 (3.7)	1.20	1.15, 1.24
Former	11,593 (6.1) / 39,790 (5.2)	1.15	1.12, 1.18	44,661 (25.2) / 159,744 (23.7)	1.11	1.09, 1.13
Depression						
Never	181,337 (95.1) / 729,834 (95.7)	(reference)		135,230 (76.2) / 527,687 (78.2)	(reference)	
Ever	9,334 (4.9) / 32,850 (4.3)	1.11	1.07, 1.14	42,131 (23.8) / 146,816 (21.8)	1.12	1.10, 1.13
Current	392 (0.2) / 1,368 (0.2)	1.09	0.93, 1.26	2,675 (1.5) / 8,939 (1.3)	1.15	1.08, 1.22
Recent	918 (0.5) / 3,036 (0.4)	1.15	1.04, 1.27	5,589 (3.2) / 18,235 (2.7)	1.17	1.13, 1.22
Former	8,024 (4.2) / 28,446 (3.7)	1.10	1.07, 1.14	33,867 (19.1) / 119,642 (17.7)	1.10	1.08, 1.12
Anxiety						
Never	187,592 (98.4) / 753,038 (98.7)	(reference)		150,534 (84.9) / 581,308 (86.2)	(reference)	
Ever	3,079 (1.6) / 9,646 (1.3)	1.23	1.17, 1.30	26,827 (15.1) / 93,195 (13.8)	1.12	1.10, 1.14
Current	103 (0.1) / 229 (0.03)	1.51	1.10, 2.06	1,150 (0.6) / 3,601 (0.5)	1.22	1.12, 1.33
Recent	199 (0.1) / 589 (0.1)	1.25	1.01, 1.55	2,547 (1.4) / 8,148 (1.2)	1.20	1.13, 1.28
Former	2,777 (1.5) / 8,828 (1.2)	1.22	1.16, 1.30	23,130 (13.0) / 81,446 (12.1)	1.10	1.08, 1.13
SSAD						
Never	186,802 (98.0) / 750,522 (98.4)	(reference)		170,597 (96.2) / 651,770 (96.6)	(reference)	
Ever	3,869 (2.0) / 12,162 (1.6)	1.24	1.18, 1.30	6,764 (3.8) / 22,733 (3.4)	1.14	1.10, 1.19
Current	134 (0.1) / 396 (0.1)	1.29	0.99, 1.67	112 (0.1) / 357 (0.1)	1.16	0.88, 1.54
Recent	358 (0.2) / 973 (0.1)	1.42	1.21, 1.67	359 (0.20) / 1,078 (0.2)	1.27	1.08, 1.48

Former	3,377 (1.8) / 10,793 (1.4)	1.22	1.16, 1.29	6,293 (3.6) / 21,298 (3.2)	1.14	1.09, 1.18

Abbreviations: CI = confidence interval; SSAD = severe stress and adjustment disorders

[a]Odds ratios are adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

Table 4. Adjusted odds ratios for previous diagnosis of mood disorder among herpes zoster cases compared with matched controls in Denmark (1997–2013) and the United Kingdom (2000–2013), by severity of mood disorder

	Denmark			The United Kingdom		
	Cases (%) / Controls (%)	**OR[a]**	**99% CI**	**Cases (%) / Controls (%)**	**OR[a]**	**99% CI**
Any mood disorder						
Never	177,196 (92.9) / 716,894 (94.0)		(reference)	75,177 (68.8) / 288,928 (71.0)		(reference)
Mild	12,885 (6.8) / 43,896 (5.8)	1.15	1.12, 1.18	33,818 (30.9) / 116,772 (28.7)	1.11	1.09, 1.14
Moderate	347 (0.2) / 1,027 (0.1)	1.28	1.09, 1.51	157 (0.1) / 478 (0.1)	1.24	0.98, 1.58
Severe	243 (0.1) / 867 (0.1)	1.05	0.87, 1.27	179 (0.2) / 637 (0.2)	1	0.80, 1.25
Depression						
Never	181,337 (95.1) / 729,834 (95.7)		(reference)	83,567 (76.4) / 318,681 (78.3)		(reference)
Mild	8,936 (4.7) / 31,450 (4.1)	1.11	1.07, 1.14	25,506 (23.3) / 87,252 (21.5)	1.11	1.08, 1.13
Moderate	212 (0.1) / 700 (0.1)	1.16	0.95, 1.43	135 (0.1) / 426 (0.1)	1.18	0.91, 1.52
Severe	186 (0.1) / 700 (0.1)	0.99	0.80, 1.23	123 (0.1) / 456 (0.1)	0.94	0.72, 1.23
Anxiety						
Never	187,592 (98.4) / 753,038 (98.7)		(reference)	93,233 (85.3) / 351,541 (86.4)		(reference)
Mild	2,976 (1.6) / 9,417 (1.2)	1.22	1.16, 1.29	15,954 (14.6) / 54,816 (13.5)	1.10	1.07, 1.13
Moderate	78 (0.04) / 149 (0.02)	1.71	1.18, 2.48	86 (0.08) / 258 (0.06)	1.23	0.89, 1.70
Severe	25 (0.01) / 80 (0.01)	1.10	0.61, 2.01	58 (0.05) / 200 (0.05)	1.02	0.69, 1.50
SSAD						
Never	186,802 (98.0) / 750,522 (98.4)		(reference)	105,325 (96.3) / 393,263 (96.7)		(reference)
Mild	3,735 (2.0) / 11,766 (1.5)	1.24	1.18, 1.30	3,984 (3.6) / 13,481 (3.3)	1.11	1.05, 1.16
Moderate	96 (0.1) / 268 (0.04)	1.37	1.01, 1.87	18 (0.02) / 53 (0.01)	1.22	0.60, 2.50
Severe	38 (0.02) / 128 (0.02)	1.11	0.69, 1.80	4 (0.002) / 18 (0.003)	0.8	0.19, 3.34

Abbreviations: CI = confidence interval; SSAD = severe stress and adjustment disorders;

[a]Odds ratios are adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

Table 5. Adjusted odds ratios[a] for current mood disorder among herpes zoster cases compared with matched controls in Denmark (1997–2013) and the United Kingdom (2000–2013) in subgroups defined by sex and age

	Denmark			The United Kingdom		
	Cases (%) / Controls (%)	**OR[a]**	**99% CI**	**Cases (%) / Controls (%)**	**OR[a]**	**99% CI**
Sex						
Women	419 (0.2) / 1,234 (0.2)	1.31	1.13, 1.52,	2,797 (1.6) / 9,132 (1.4)	1.24	1.17, 1.31
Men	166 (0.1) / 633 (0.1)	0.93	0.73, 1.16	981 (0.6) / 3,268 (0.5)	1.07	0.97, 1.17
Age, years						
<50	128 (0.1) / 386 (0.1)	1.22	0.93, 1.61	1,415 (0.8) / 4,352 (0.6)	1.28	1.17, 1.38
50–59	108 (0.1) / 365 (0.05)	1.08	0.80, 1.44	833 (0.5) / 2,720 (0.4)	1.21	1.09, 1.35
60–69	110 (0.1) / 290 (0.04)	1.41	1.05, 1.90	638 (0.4) / 2,178 (0.3)	1.13	1.01, 1.28
≥70	260 (0.1) / 903 (0.1)	1.11	0.92, 1.35	892 (0.5) / 3,150 (0.5)	1.09	0.98, 1.20

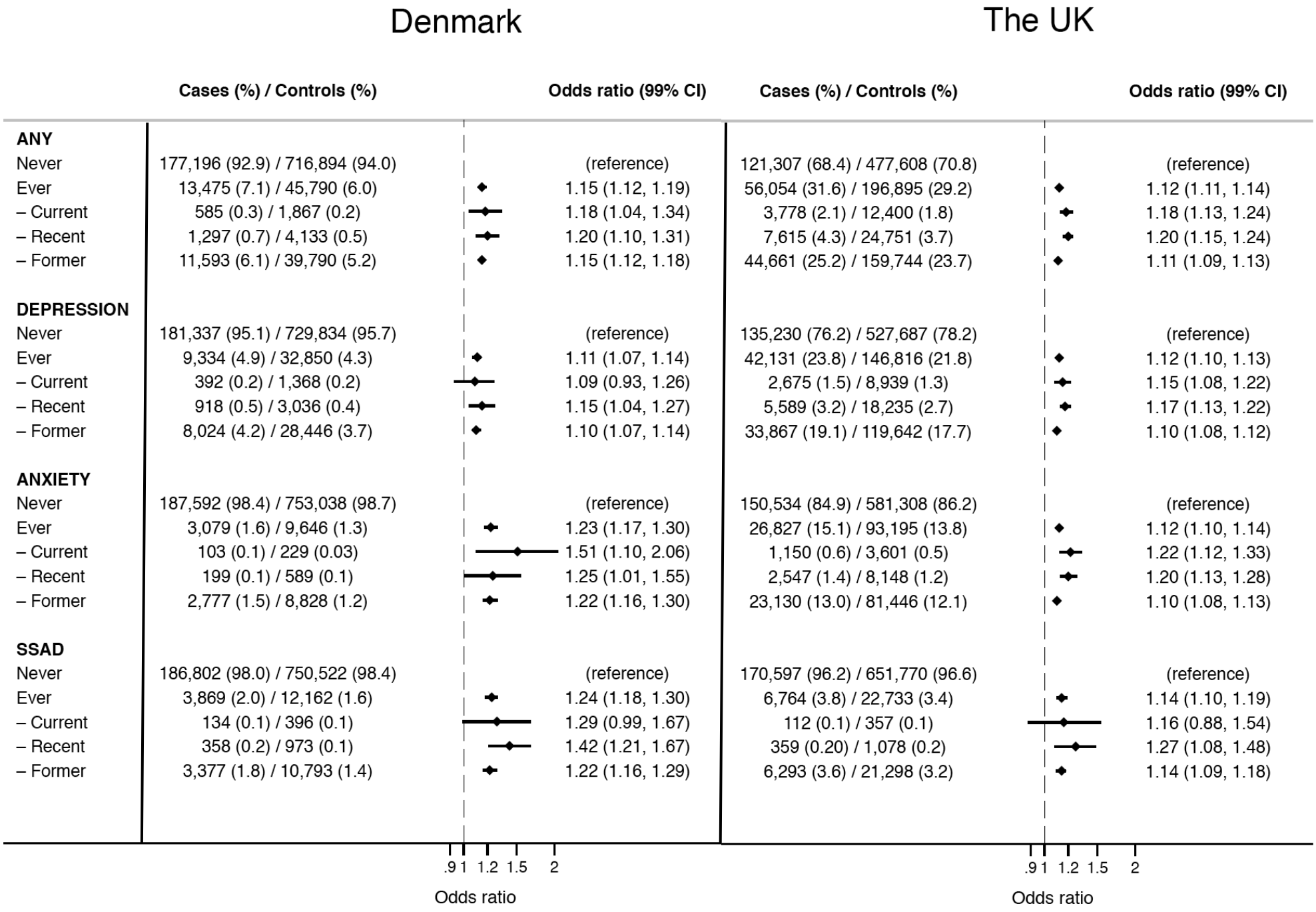
Abbreviation: CI = confidence interval

[a]Odds ratios are adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

Table 6. Age-Specific Rate of Herpes Zoster per 1,000 Person-Years (99% Confidence Interval) in Persons With Any Mood disorder in Denmark (1997–2013) and the United Kingdom (2000–2013)

	Age group							
	<50 years		50–59 years		60–69 years		≥70 years	
	Rate	99% CI	Rate	99% CI	Rate	99% CI	Rate	99% CI
Reference[a]	2.08	1.74, 2.49	4.37	3.72, 5.12	6.69	5.76, 7.76	8.84	7.49, 10.43
Denmark	2.73	2.15, 3.47	5.29	3.91, 7.15	7.49	5.59, 10.02	9.47	7.02, 12.79
The UK	2.54	2.06, 3.13	4.92	3.89, 6.22	7.32	5.85, 9.15	9.40	7.42, 11.92

[a]UK general population, 2010


Denmark
The UK
Cases (%) / Controls (%)
Odds ratio (99% CI)
Cases (%) / Controls (%)
Odds ratio (99% CI)
ANY
Never 177,196 (92.9) / 716,894 (94.0) (reference) 121,307 (68.4) / 477,608 (70.8) (reference)
Ever 13,475 (7.1) / 45,790 (6.0) 1.15 (1.12, 1.19) 56,054 (31.6) / 196,895 (29.2) 1.12 (1.11, 1.14)
– Current 585 (0.3) / 1,867 (0.2) 1.18 (1.04, 1.34) 3,778 (2.1) / 12,400 (1.8) 1.18 (1.13, 1.24)
– Recent 1,297 (0.7) / 4,133 (0.5) 1.20 (1.10, 1.31) 7,615 (4.3) / 24,751 (3.7) 1.20 (1.15, 1.24)
– Former 11,593 (6.1) / 39,790 (5.2) 1.15 (1.12, 1.18) 44,661 (25.2) / 159,744 (23.7) 1.11 (1.09, 1.13)
DEPRESSION
Never 181,337 (95.1) / 729,834 (95.7) (reference) 135,230 (76.2) / 527,687 (78.2) (reference)
Ever 9,334 (4.9) / 32,850 (4.3) 1.11 (1.07, 1.14) 42,131 (23.8) / 146,816 (21.8) 1.12 (1.10, 1.13)
– Current 392 (0.2) / 1,368 (0.2) 1.09 (0.93, 1.26) 2,675 (1.5) / 8,939 (1.3) 1.15 (1.08, 1.22)
– Recent 918 (0.5) / 3,036 (0.4) 1.15 (1.04, 1.27) 5,589 (3.2) / 18,235 (2.7) 1.17 (1.13, 1.22)
– Former 8,024 (4.2) / 28,446 (3.7) 1.10 (1.07, 1.14) 33,867 (19.1) / 119,642 (17.7) 1.10 (1.08, 1.12)
ANXIETY
Never 187,592 (98.4) / 753,038 (98.7) (reference) 150,534 (84.9) / 581,308 (86.2) (reference)
Ever 3,079 (1.6) / 9,646 (1.3) 1.23 (1.17, 1.30) 26,827 (15.1) / 93,195 (13.8) 1.12 (1.10, 1.14)
– Current 103 (0.1) / 229 (0.03) 1.51 (1.10, 2.06) 1,150 (0.6) / 3,601 (0.5) 1.22 (1.12, 1.33)
– Recent 199 (0.1) / 589 (0.1) 1.25 (1.01, 1.55) 2,547 (1.4) / 8,148 (1.2) 1.20 (1.13, 1.28)
– Former 2,777 (1.5) / 8,828 (1.2) 1.22 (1.16, 1.30) 23,130 (13.0) / 81,446 (12.1) 1.10 (1.08, 1.13)
SSAD
Never 186,802 (98.0) / 750,522 (98.4) (reference) 170,597 (96.2) / 651,770 (96.6) (reference)
Ever 3,869 (2.0) / 12,162 (1.6) 1.24 (1.18, 1.30) 6,764 (3.8) / 22,733 (3.4) 1.14 (1.10, 1.19)
– Current 134 (0.1) / 396 (0.1) 1.29 (0.99, 1.67) 112 (0.1) / 357 (0.1) 1.16 (0.88, 1.54)
– Recent 358 (0.2) / 973 (0.1) 1.42 (1.21, 1.67) 359 (0.20) / 1,078 (0.2) 1.27 (1.08, 1.48)
– Former 3,377 (1.8) / 10,793 (1.4) 1.22 (1.16, 1.29) 6,293 (3.6) / 21,298 (3.2) 1.14 (1.09, 1.18)
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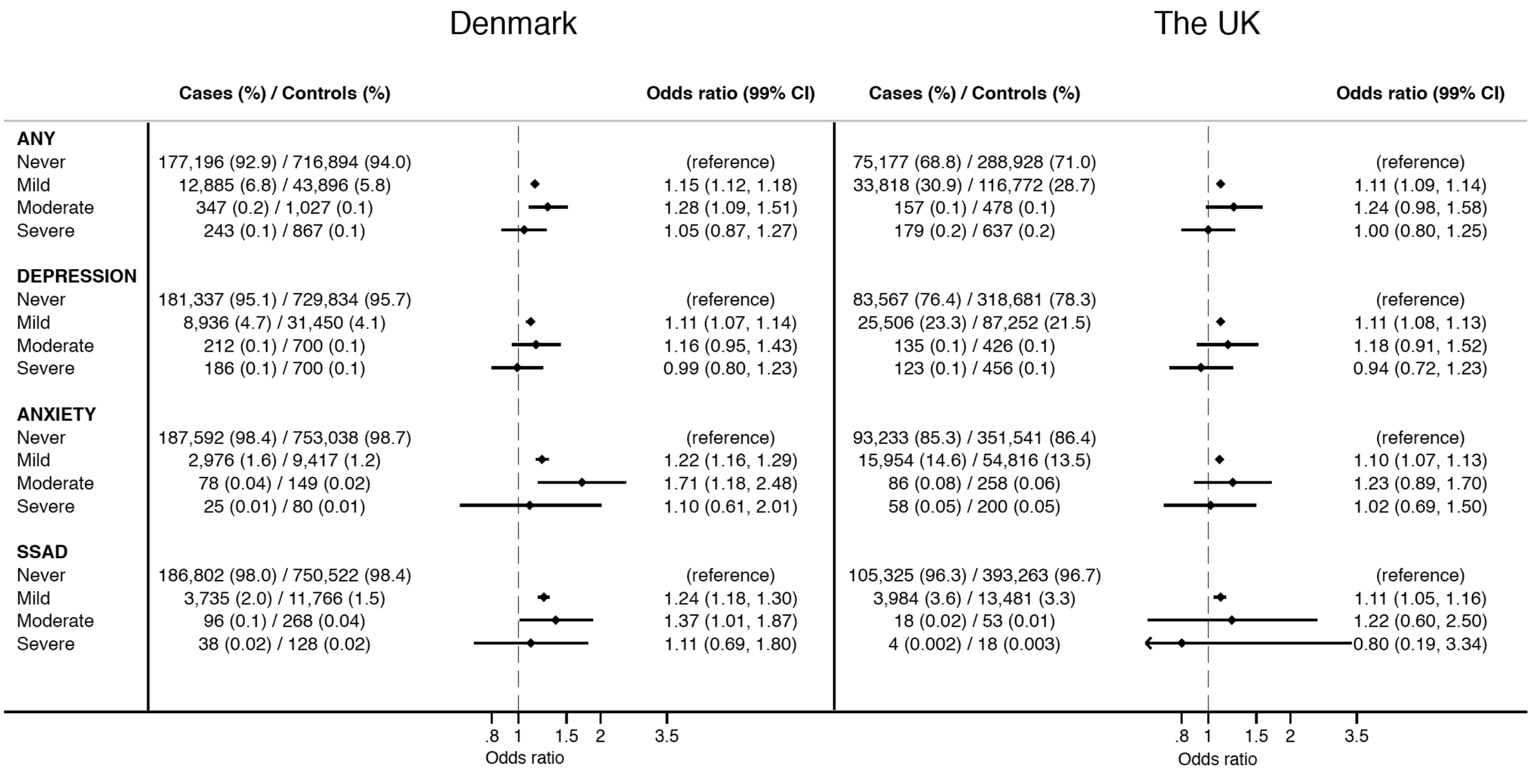
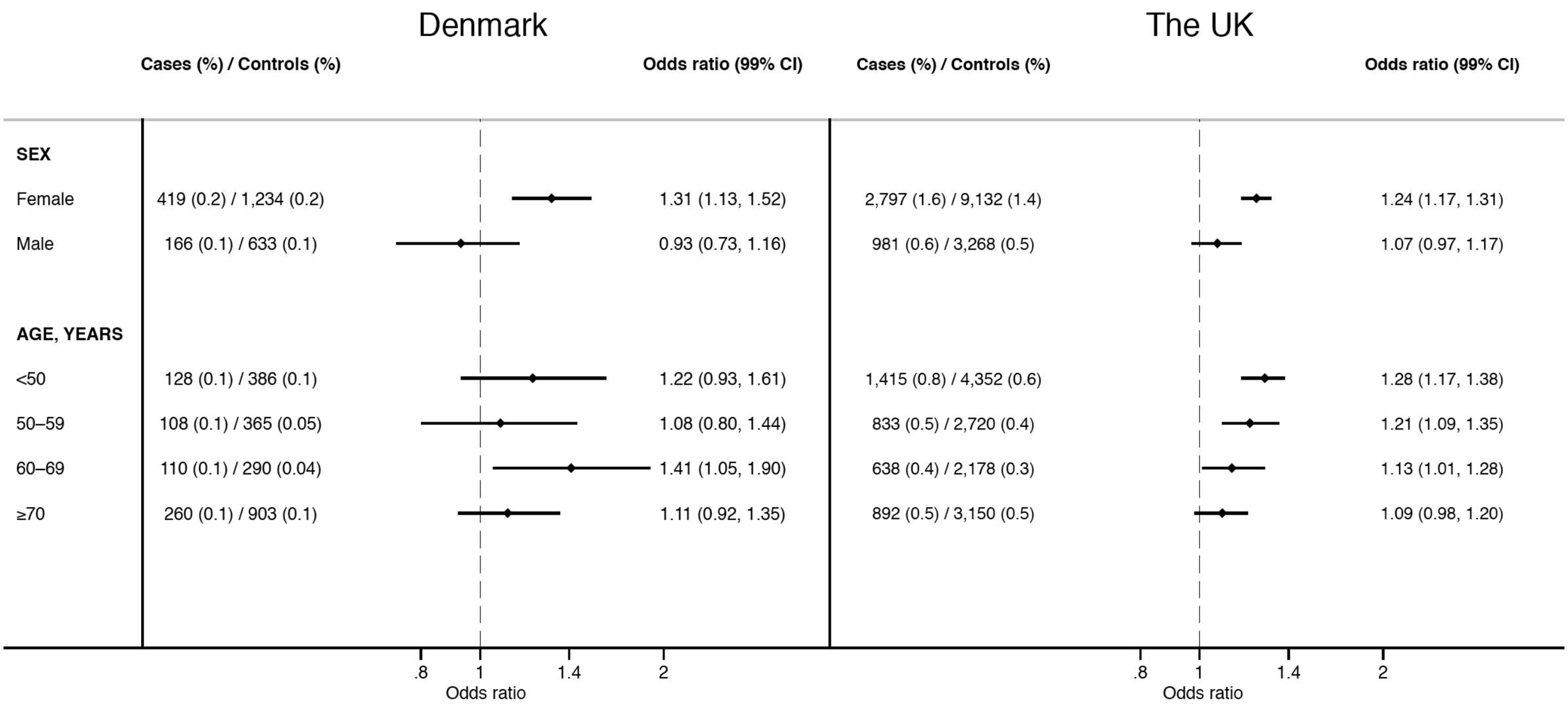
Odds ratio
.9 1 1.2 1.5 2
Odds ratio


Denmark
The UK
Cases (%) / Controls (%)
Odds ratio (99% CI)
Cases (%) / Controls (%)
Odds ratio (99% CI)
ANY
Never
177,196 (92.9) / 716,894 (94.0)
(reference)
75,177 (68.8) / 288,928 (71.0)
(reference)
Mild
12,885 (6.8) / 43,896 (5.8)
1.15 (1.12, 1.18)
33,818 (30.9) / 116,772 (28.7)
1.11 (1.09, 1.14)
Moderate
347 (0.2) / 1,027 (0.1)
1.28 (1.09, 1.51)
157 (0.1) / 478 (0.1)
1.24 (0.98, 1.58)
Severe
243 (0.1) / 867 (0.1)
1.05 (0.87, 1.27)
179 (0.2) / 637 (0.2)
1.00 (0.80, 1.25)
DEPRESSION
Never
181,337 (95.1) / 729,834 (95.7)
(reference)
83,567 (76.4) / 318,681 (78.3)
(reference)
Mild
8,936 (4.7) / 31,450 (4.1)
1.11 (1.07, 1.14)
25,506 (23.3) / 87,252 (21.5)
1.11 (1.08, 1.13)
Moderate
212 (0.1) / 700 (0.1)
1.16 (0.95, 1.43)
135 (0.1) / 426 (0.1)
1.18 (0.91, 1.52)
Severe
186 (0.1) / 700 (0.1)
0.99 (0.80, 1.23)
123 (0.1) / 456 (0.1)
0.94 (0.72, 1.23)
ANXIETY
Never
187,592 (98.4) / 753,038 (98.7)
(reference)
93,233 (85.3) / 351,541 (86.4)
(reference)
Mild
2,976 (1.6) / 9,417 (1.2)
1.22 (1.16, 1.29)
15,954 (14.6) / 54,816 (13.5)
1.10 (1.07, 1.13)
Moderate
78 (0.04) / 149 (0.02)
1.71 (1.18, 2.48)
86 (0.08) / 258 (0.06)
1.23 (0.89, 1.70)
Severe
25 (0.01) / 80 (0.01)
1.10 (0.61, 2.01)
58 (0.05) / 200 (0.05)
1.02 (0.69, 1.50)
SSAD
Never
186,802 (98.0) / 750,522 (98.4)
(reference)
105,325 (96.3) / 393,263 (96.7)
(reference)
Mild
3,735 (2.0) / 11,766 (1.5)
1.24 (1.18, 1.30)
3,984 (3.6) / 13,481 (3.3)
1.11 (1.05, 1.16)
Moderate
96 (0.1) / 268 (0.04)
1.37 (1.01, 1.87)
18 (0.02) / 53 (0.01)
1.22 (0.60, 2.50)
Severe
38 (0.02) / 128 (0.02)
1.11 (0.69, 1.80)
4 (0.002) / 18 (0.003)
0.80 (0.19, 3.34)
.8
1
1.5
2
3.5
Odds ratio
.8
1
1.5
2
3.5
Odds ratio


Denmark
The UK
Cases (%) / Controls (%)
Odds ratio (99% CI)
Cases (%) / Controls (%)
Odds ratio (99% CI)
SEX
Female
419 (0.2) / 1,234 (0.2)
1.31 (1.13, 1.52)
2,797 (1.6) / 9,132 (1.4)
1.24 (1.17, 1.31)
Male
166 (0.1) / 633 (0.1)
0.93 (0.73, 1.16)
981 (0.6) / 3,268 (0.5)
1.07 (0.97, 1.17)
AGE, YEARS
<50
128 (0.1) / 386 (0.1)
1.22 (0.93, 1.61)
1,415 (0.8) / 4,352 (0.6)
1.28 (1.17, 1.38)
50–59
108 (0.1) / 365 (0.05)
1.08 (0.80, 1.44)
833 (0.5) / 2,720 (0.4)
1.21 (1.09, 1.35)
60–69
110 (0.1) / 290 (0.04)
1.41 (1.05, 1.90)
638 (0.4) / 2,178 (0.3)
1.13 (1.01, 1.28)
≥70
260 (0.1) / 903 (0.1)
1.11 (0.92, 1.35)
892 (0.5) / 3,150 (0.5)
1.09 (0.98, 1.20)
.8
1
1.4
2
Odds ratio
.8
1
1.4
2
Odds ratio

Supplementary Appendix 1. Description of Additional Analyses

This file provides a description of additional subgroup, sensitivity, and *post hoc* analyses for the association between mood disorders and herpes zoster (HZ). The results of these analyses, including the distribution of variables used in sensitivity analyses, are shown in Supplementary Appendix 2.

Subgroup analyses

To examine if the association between mood disorder and HZ was more pronounced for persons with new-onset, we performed a subgroup analyses where we subdivided the current group based on whether their first-time record of mood disorder occurred ≤90 days before the index date or not.

Sensitivity analyses

This file provides a description of the sensitivity analyses performed to address (i) the robustness of the exposure definitions, (ii) potential misclassification of HZ in the Danish data due to use of antivirals for other indications, (iii) the potential impact of marketing of the HZ vaccine, and (iv) potential confounding from lifestyle and socioeconomic factors.

We performed five sensitivity analyses of our definitions of exposure to mood disorder. First, in an attempt to capture persons treated for mood disorder outside the hospital-based setting in Denmark, we included previous prescriptions for an antidepressant as a proxy for diagnosis. Second, assuming that patients treated with antidepressants had more severe disease than those not receiving treatment with antidepressants, inpatient care, or referral to mental health service, we examined the following alternative severity definition based on records within the past 90 days: very severe (requiring inpatient admission), moderate (persons with any other hospital contact for the condition in Denmark; persons with referral from general practice to a mental health service in the UK), moderate (requiring prescription for an antidepressant), or mild (remaining patients). Third, we consecutively varied the cut-off between the 'current' and 'recent' categories of mood disorder from 90 days to 7, 14, 30, and lastly 180 days. Fourth, we repeated the main analysis after excluding those with only possible diagnosis codes (*e.g.*, 'suspected depression') or codes for subtypes considered secondary to other conditions (*e.g.*, depression or anxiety related to organic disease, dementia, or pregnancy). Finally, we performed analyses considering each mood disorder exclusively, *i.e.*, excluding persons with codes for more than one subtype of mood disorder. In all sensitivity analyses including data on antidepressants, we disregarded prescriptions recorded within two weeks before the index date to avoid including treatment for HZ-associated pain.

Indication codes have been available in the Danish National Prescription Registry since April 2004. To increase the specificity of the prescription-based algorithm used to identify HZ cases in Danish primary care, we therefore performed a sensitivity analysis excluding cases without an indication specifically mentioning HZ. We did not to utilize these codes in the main analyses, because they were often unspecific (*e.g.*, stating 'herpes infection') and because they were available for only 77% of cases included based on dispensing of an antiviral prescription since introduction of the codes in the prescription registry.

To avoid any effect of HZ vaccination on the findings, we repeated the analyses after excluding case-control sets with index date after marketing of the HZ vaccine on 31 August, 2014 in the UK. The vaccine was not available in Denmark during the study.

Finally, we performed two analyses to further address potential confounding. We adjusted for individual-level measures of socioeconomic status, using the highest achieved education (short [≤10 years], medium [>10–15 years], long [>15 years]) in Denmark (available for 90% of participants) and quintiles of the Index of Multiple Deprivation score mapped to residence postcode in the UK (available for 62% of participants). We also examined the impact of adjusting for smoking status (current smoker, ex-smoker, or non-smoker), alcohol consumption (current drinker, ex-drinker, non-drinker), and body mass index (underweight [(<18.5 kg/m^2], normal weight [18.5–24.9 kg/m^2], overweight [25–29.9 kg/m^2], obese [(≥30 kg/m^2] [1]) in the UK data. Such data are not routinely collected in Denmark. We pragmatically defined lifestyle factors based on records closest to the index date, giving priority to the nearest record within –1 year to +1 months of the index date, followed by +1 months to +1 years, before –1 year, and finally, +1 year from index date [2]. We used both the additional details file and Read codes in the Clinical Practice Research Datalink, except for BMI, which is rarely recorded using Read codes. Missingness of at least one lifestyle variable was observed for 14% of participants and was more frequent among cases, males, persons at the extremes of the age range, and those without HZ risk factors. In this analysis, we used the complete-case dataset. This approach leads to asymptotically unbiased estimates if missingness is conditionally independent on the outcome [3], *i.e.*, if there is no association between missing data on lifestyle variables and diagnosis of HZ. We considered this assumption more plausible than that required for multiple imputation (*i.e.*, that data are "missing at random"), because recording of lifestyle factors likely depends on the actual value of the factor.

Post hoc analyses

Against our expectations, we found the lowest ORs for severe mood disorders. We suspected that this result could be explained by underascertainment of HZ diagnoses made as coincidental findings during hospital follow-up of patients recently admitted with mood disorder. In an attempt to explore this suspicion further, we performed a *post hoc* analysis where we included secondary hospital diagnoses of HZ in the case definitions. Of note, the original decision to include only primary hospital diagnoses was based on (i) the importance of a precise date of HZ diagnosis for the timing analysis and (ii) an assumption that the admission date would be more accurate for primary diagnoses (where HZ is the main reason for contact) than for secondary diagnoses (where HZ may have appeared at any time between start and end dates for a hospital contact).

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Supplementary Appendix 2. Additional results

Contents

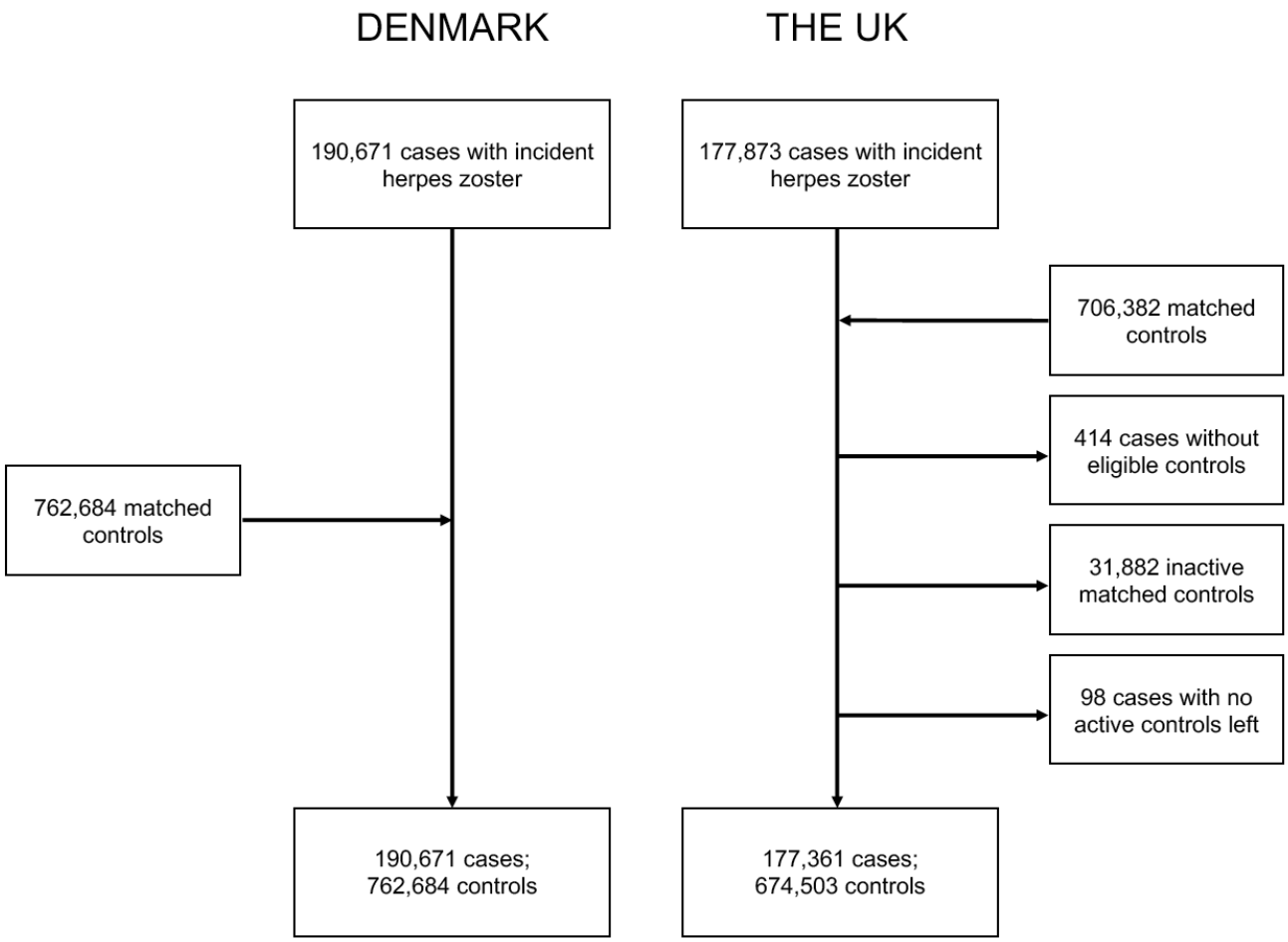

Figure 1. Flowchart for the study.

Notes: Inclusion criteria for case patients and controls were no previous Read Code or *International Classification of Diseases*, 10th revision, code for postherpetic neuralgia; age ≥40 years and no previous prescription for systemic acyclovir, valacyclovir, or famciclovir (Denmark only); and registration with current general practice for ≥12 months before the index date (United Kingdom only).

Table e1. Odds ratios for the association between mood disorders and herpes zoster, by timing.

	Denmark		UK	
	Unadjusted odds ratio (99% CI)	**Adjusted odds ratio (99% CI)***	**Unadjusted odds ratio (99% CI)**	**Adjusted odds ratio (99% CI)***
Any				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.19 (1.16–1.22)	1.15 (1.12–1.19)	1.15 (1.13–1.16)	1.12 (1.11–1.14)
Current	1.26 (1.12–1.42)	1.18 (1.04–1.34)	1.22 (1.16–1.28)	1.18 (1.13–1.24)
– First-time	1.33 (1.13–1.57)	1.21 (1.02–1.43)	1.16 (1.07–1.27)	1.13 (1.03–1.23)
– Not first-time	1.20 (1.00–1.44)	1.15 (0.96–1.38)	1.25 (1.18–1.33)	1.21 (1.14–1.28)
Recent	1.27 (1.17–1.38)	1.20 (1.10–1.31)	1.24 (1.19–1.28)	1.20 (1.15–1.24)
Former	1.18 (1.15–1.21)	1.15 (1.12–1.18)	1.13 (1.11–1.15)	1.11 (1.09–1.13)
Depression				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.14 (1.11–1.18)	1.11 (1.07–1.14)	1.14 (1.12–1.16)	1.12 (1.10–1.13)
Current	1.16 (1.00–1.34)	1.09 (0.93–1.26)	1.19 (1.12–1.26)	1.15 (1.08–1.22)
– First-time	1.20 (0.97–1.49)	1.12 (0.90–1.39)	1.11 (1.00–1.25)	1.08 (0.97–1.21)
– Not first-time	1.12 (0.91–1.37)	1.06 (0.86–1.30)	1.21 (1.14–1.30)	1.17 (1.10–1.26)
Recent	1.22 (1.11–1.34)	1.15 (1.04–1.27)	1.22 (1.17–1.27)	1.17 (1.13–1.22)
Former	1.14 (1.10–1.17)	1.10 (1.07–1.14)	1.13 (1.11–1.15)	1.10 (1.08–1.12)
Anxiety				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.28 (1.21–1.35)	1.23 (1.17–1.30)	1.13 (1.11–1.16)	1.12 (1.10–1.14)
Current	1.81 (1.33–2.45)	1.51 (1.10–2.06)	1.25 (1.14–1.36)	1.22 (1.12–1.33)
– First-time	2.10 (1.44–3.06)	1.62 (1.10–2.39)	1.19 (1.03–1.38)	1.17 (1.01–1.35)
– Not first-time	1.38 (0.81–2.34)	1.32 (0.78–2.26)	1.28 (1.15–1.43)	1.25 (1.12–1.40)
Recent	1.36 (1.10–1.68)	1.25 (1.01–1.55)	1.23 (1.16–1.30)	1.20 (1.13–1.28)
Former	1.26 (1.19–1.34)	1.22 (1.16–1.30)	1.12 (1.10–1.14)	1.10 (1.08–1.13)
SSAD				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.28 (1.22–1.34)	1.24 (1.18–1.30)	1.16 (1.11–1.20)	1.14 (1.10–1.19)
Current	1.36 (1.05–1.76)	1.29 (0.99–1.67)	1.20 (0.90–1.58)	1.16 (0.88–1.54)
– First-time	1.16 (0.83–1.63)	1.08 (0.77–1.52)	1.16 (0.83–1.61)	1.12 (0.80–1.56)
– Not first-time	1.75 (1.17–2.63)	1.69 (1.12–2.54)	1.31 (0.78–2.20)	1.28 (0.75–2.16)
Recent	1.48 (1.26–1.74)	1.42 (1.21–1.67)	1.28 (1.09–1.50)	1.27 (1.08–1.48)
Former	1.26 (1.20–1.33)	1.22 (1.16–1.29)	1.15 (1.11–1.20)	1.14 (1.09–1.18)

Abbreviations: CI = confidence interval; SSAD = severe stress and adjustment disorder

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, asthma, chronic kidney disease, diabetes, inhaled corticosteroids, solid organ transplantation, HIV infection, leukemia, lymphoma, myeloma, hematopoietic stem cell/bone marrow transplantation, other unspecified cellular immune deficiencies, oral glucocorticoids, and other immunosuppressive treatment.

Table e2. Odds ratios for the association between mood disorders and herpes zoster, by severity.

	Denmark		The UK	
	Unadjusted odds ratio (99% CI)	**Adjusted odds ratio (99% CI)***	**Unadjusted odds ratio (99% CI)**	**Adjusted odds ratio (99% CI)***
Any				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.19 (1.16–1.22)	1.15 (1.12–1.18)	1.14 (1.12–1.16)	1.11 (1.09–1.14)
Moderate	1.37 (1.17–1.61)	1.28 (1.09–1.51)	1.28 (1.01–1.63)	1.24 (0.98–1.58)
Severe	1.14 (0.94–1.37)	1.05 (0.87–1.27)	1.10 (0.88–1.37)	1.00 (0.80–1.25)
Depression				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.14 (1.11–1.18)	1.11 (1.07–1.14)	1.14 (1.11–1.16)	1.11 (1.08–1.13)
Moderate	1.22 (1.00–1.50)	1.16 (0.95–1.43)	1.22 (0.95–1.58)	1.18 (0.91–1.52)
Severe	1.07 (0.87–1.33)	0.99 (0.80–1.23)	1.05 (0.80–1.36)	0.94 (0.72–1.23)
Anxiety				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.27 (1.20–1.34)	1.22 (1.16–1.29)	1.12 (1.09–1.15)	1.10 (1.07–1.13)
Moderate	2.10 (1.47–3.02)	1.71 (1.18–2.48)	1.27 (0.92–1.75)	1.23 (0.89–1.70)
Severe	1.25 (0.69–2.27)	1.10 (0.61–2.01)	1.10 (0.75–1.62)	1.02 (0.69–1.50)
SSAD				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.28 (1.22–1.34)	1.24 (1.18–1.30)	1.12 (1.07–1.18)	1.11 (1.05–1.16)
Moderate	1.44 (1.06–1.96)	1.37 (1.01–1.87)	1.25 (0.62–2.54)	1.22 (0.60–2.50)
Severe	1.19 (0.74–1.92)	1.11 (0.69–1.80)	0.79 (0.19–3.30)	0.80 (0.19–3.34)

Abbreviations: CI = confidence interval; SSAD = severe stress and adjustment disorder

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, asthma, chronic kidney disease, diabetes, inhaled corticosteroids, solid organ transplantation, HIV infection, leukemia, lymphoma, myeloma, hematopoietic stem cell/bone marrow transplantation, other unspecified cellular immune deficiencies, oral glucocorticoids, and other immunosuppressive treatment.

Table e3. Odds ratios for the association between current mood disorders and herpes zoster, subgroup analysis.

	Denmark				The UK			
	Cases, n (%)	Controls, n (%)	Unadjusted odds ratio (99% CI)	Adjusted odds ratio (99% CI)*	Cases, n (%)	Controls, n (%)	Unadjusted odds ratio (99% CI)	Adjusted odds ratio (99% CI)*
Any								
Sex								
Female	419 (0.2)	1234 (0.2)	1.40 (1.21–1.61)	1.31 (1.13–1.52)	2798 (1.58)	9132 (1.35)	1.27 (1.20–1.35)	1.24 (1.17–1.31)
Male	166 (0.1)	633 (0.1)	1.04 (0.83–1.30)	0.93 (0.73–1.16)	981 (0.55)	3269 (0.48)	1.11 (1.01–1.22)	1.07 (0.97–1.17)
Age, years								
<50	122 (0.1)	380 (0.1)	1.31 (1.00–1.72)	1.26 (0.97–1.65)	1415 (0.80)	4352 (0.65)	1.30 (1.20–1.41)	1.28 (1.17–1.38)
50–59	106 (0.1)	355 (0.0)	1.21 (0.91–1.62)	1.07 (0.80–1.43)	833 (0.47)	2720 (0.40)	1.24 (1.12–1.38)	1.21 (1.09–1.35)
60–69	109 (0.1)	280 (0.0)	1.57 (1.18–2.11)	1.38 (1.02–1.85)	638 (0.36)	2178 (0.32)	1.20 (1.07–1.35)	1.13 (1.01–1.28)
≥70	248 (0.1)	852 (0.1)	1.17 (0.97–1.41)	1.10 (0.92–1.33)	892 (0.50)	3150 (0.47)	1.13 (1.02–1.25)	1.09 (0.98–1.20)
Depression								
Sex								
Female	276 (0.1)	903 (0.1)	1.24 (1.04–1.49)	1.19 (0.99–1.42)	1966 (1.11)	6557 (0.97)	1.23 (1.15–1.32)	1.19 (1.12–1.28)
Male	116 (0.1)	465 (0.1)	0.99 (0.76–1.29)	0.89 (0.67–1.16)	709 (0.40)	2383 (0.35)	1.09 (0.98–1.22)	1.04 (0.93–1.17)
Age, years								
<50	59 (0.0)	191 (0.0)	1.25 (0.85–1.83)	1.16 (0.79–1.72)	1019 (0.57)	3136 (0.46)	1.29 (1.17–1.42)	1.26 (1.14–1.38)
50–59	61 (0.0)	229 (0.0)	1.07 (0.74–1.56)	0.98 (0.67–1.43)	586 (0.33)	1961 (0.29)	1.19 (1.06–1.35)	1.17 (1.03–1.32)
60–69	68 (0.0)	207 (0.0)	1.32 (0.92–1.90)	1.21 (0.84–1.74)	445 (0.25)	1512 (0.22)	1.19 (1.03–1.37)	1.12 (0.97–1.29)
≥70	204 (0.1)	741 (0.1)	1.11 (0.90–1.36)	1.06 (0.86–1.30)	626 (0.35)	2330 (0.35)	1.06 (0.94–1.20)	1.02 (0.91–1.15)
Anxiety								
Sex								
Female	76 (0.0)	145 (0.0)	2.12 (1.47–3.05)	1.86 (1.28–2.69)	853 (0.48)	2692 (0.40)	1.27 (1.15–1.41)	1.24 (1.12–1.38)
Male	27 (0.0)	84 (0.0)	1.28 (0.72–2.27)	0.96 (0.53–1.73)	297 (0.17)	909 (0.13)	1.19 (1.00–1.41)	1.16 (0.98–1.38)
Age, years								
<50	30 (0.0)	69 (0.0)	1.76 (1.00–3.09)	1.57 (0.88–2.79)	403 (0.23)	1269 (0.19)	1.21 (1.04–1.41)	1.21 (1.04–1.40)
50–59	21 (0.0)	50 (0.0)	1.69 (0.86–3.30)	1.20 (0.59–2.44)	251 (0.14)	774 (0.11)	1.28 (1.06–1.54)	1.24 (1.03–1.50)
60–69	24 (0.0)	31 (0.0)	3.11 (1.54–6.26)	2.38 (1.15–4.94)	208 (0.12)	697 (0.10)	1.20 (0.98–1.47)	1.15 (0.94–1.42)
≥70	28 (0.0)	79 (0.0)	1.42 (0.81–2.51)	1.23 (0.69–2.19)	288 (0.16)	861 (0.13)	1.32 (1.11–1.58)	1.28 (1.08–1.53)
SSAD								
Sex								
Female	96 (0.1)	272 (0.0)	1.42 (1.05–1.93)	1.33 (0.98–1.81)	88 (0.05)	247 (0.04)	1.39 (1.01–1.91)	1.34 (0.97–1.85)
Male	38 (0.0)	124 (0.0)	1.23 (0.76–1.98)	1.21 (0.75–1.96)	24 (0.01)	110 (0.02)	0.79 (0.44–1.42)	0.78 (0.44–1.41)
Age, years								
<50	50 (0.0)	157 (0.0)	1.29 (0.85–1.96)	1.22 (0.80–1.86)	50 (0.03)	137 (0.02)	1.35 (0.88–2.07)	1.33 (0.87–2.05)
50–59	34 (0.0)	116 (0.0)	1.18 (0.71–1.95)	1.06 (0.64–1.77)	34 (0.02)	88 (0.01)	1.50 (0.89–2.53)	1.51 (0.89–2.54)
60–69	26 (0.0)	58 (0.0)	1.80 (0.98–3.30)	1.71 (0.92–3.17)	16 (0.01)	60 (0.01)	1.05 (0.51–2.17)	0.91 (0.44–1.91)
≥70	24 (0.0)	65 (0.0)	1.48 (0.80–2.74)	1.42 (0.76–2.64)	12 (0.01)	72 (0.01)	0.65 (0.29–1.46)	0.65 (0.29–1.47)

Abbreviations: CI = confidence interval; SSAD = severe stress and adjustment disorder

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, asthma, chronic kidney disease, diabetes, inhaled corticosteroids, solid organ transplantation, HIV infection, leukemia, lymphoma, myeloma, hematopoietic stem cell/bone marrow transplantation, other unspecified cellular immune deficiencies, oral glucocorticoids, and other immunosuppressive treatment.

Table e4. Odds ratios for the association between any mood disorder and herpes zoster in Denmark, including antidepressant prescriptions as a proxy for mood disorder in order to capture patients treated in outside the hospital-based setting.

	Cases, n (%)	Controls, n (%)	Unadjusted odds ratio (99% CI)	Adjusted odds ratio (99% CI)*
Timing				
Never	139190 (73.0)	593665 (77.8)	(reference)	(reference)
Ever	51481 (27.0)	169019 (22.2)	1.31 (1.29–1.33)	1.26 (1.24–1.28)
Current	17859 (9.4)	57923 (7.6)	1.32 (1.29–1.36)	1.26 (1.23–1.29)
Recent	7893 (4.1)	24978 (3.3)	1.35 (1.31–1.40)	1.30 (1.25–1.34)
Former	25729 (13.5)	86118 (11.3)	1.28 (1.26–1.31)	1.25 (1.22–1.27)
Severity				
Never	139190 (73.0)	593665 (77.8)	(reference)	(reference)
Mild	33622 (17.6)	111090 (14.6)	1.30 (1.27–1.32)	1.26 (1.24–1.28)
Moderate	17269 (9.1)	56035 (7.3)	1.32 (1.29–1.36)	1.26 (1.23–1.29)
Severe	347 (0.2)	1027 (0.1)	1.45 (1.23–1.70)	1.35 (1.15–1.59)
Very severe	243 (0.1)	867 (0.1)	1.20 (1.00–1.45)	1.11 (0.92–1.34)

Abbreviations: CI = confidence interval

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

Table e5. Odds ratios for the association between mood disorders and herpes zoster, by severity. Sensitivity analysis incorporating data on treatment with antidepressants in the severity definition of mood disorders.†

	Denmark				UK			
	Cases, n (%)	Controls, n (%)	Unadjusted odds ratio (99% CI)	Adjusted odds ratio (99% CI)†	Cases, n (%)	Controls, n (%)	Unadjusted odds ratio (99% CI)	Adjusted odds ratio (99% CI)†
Any								
Never	177196 (92.9)	716894 (94.0)	(reference)	(reference)	75177 (68.8)	288928 (71.0)	(reference)	(reference)
Mild	7705 (4.0)	26638 (3.5)	1.17 (1.13–1.21)	1.14 (1.10–1.18)	27715(25.35)	96895(23.82)	1.12 (1.10–1.15)	1.10 (1.08–1.13)
Moderate	5180 (2.7)	17258 (2.3)	1.22 (1.17–1.27)	1.17 (1.12–1.22)	6103(5.58)	19877(4.89)	1.21 (1.16–1.26)	1.17 (1.12–1.22)
Severe	347 (0.2)	1027 (0.1)	1.37 (1.17–1.61)	1.28 (1.09–1.51)	157(0.14)	478(0.12)	1.28 (1.01–1.63)	1.24 (0.98–1.58)
Very severe	243 (0.1)	867 (0.1)	1.14 (0.94–1.37)	1.05 (0.87–1.27)	179(0.16)	637(0.16)	1.10 (0.88–1.37)	1.00 (0.80–1.25)
Depression								
Never	181337 (95.1)	729834 (95.7)	(reference)	(reference)	83567 (76.4)	318681 (78.3)	(reference)	(reference)
Mild	4677 (2.5)	16920 (2.2)	1.11 (1.07–1.16)	1.09 (1.04–1.13)	20132(18.41)	69845(17.17)	1.12 (1.09–1.15)	1.10 (1.07–1.12)
Moderate	4259 (2.2)	14530 (1.9)	1.18 (1.13–1.24)	1.14 (1.08–1.19)	5374(4.92)	17407(4.28)	1.20 (1.15–1.26)	1.16 (1.11–1.21)
Severe	212 (0.1)	700 (0.1)	1.22 (1.00–1.50)	1.16 (0.95–1.43)	135(0.12)	426(0.10)	1.22 (0.95–1.58)	1.18 (0.91–1.52)
Very severe	186 (0.1)	700 (0.1)	1.07 (0.87–1.32)	0.99 (0.80–1.23)	123(0.11)	456(0.11)	1.05 (0.80–1.36)	0.94 (0.72–1.23)
Anxiety								
Never	187592 (98.4)	753038 (98.7)	(reference)	(reference)	93233 (85.3)	351541 (86.4)	(reference)	(reference)
Mild	1815 (1.0)	5842 (0.8)	1.25 (1.16–1.34)	1.21 (1.13–1.30)	12815(11.72)	44625(10.97)	1.10 (1.07–1.13)	1.09 (1.06–1.12)
Moderate	1161 (0.6)	3575 (0.5)	1.30 (1.20–1.42)	1.24 (1.14–1.36)	3139(2.87)	10191(2.51)	1.19 (1.12–1.25)	1.16 (1.10–1.22)
Severe	78 (0.0)	149 (0.0)	2.10 (1.47–3.02)	1.71 (1.18–2.48)	86(0.08)	258(0.06)	1.27 (0.92–1.75)	1.23 (0.89–1.71)
Very severe	25 (0.0)	80 (0.0)	1.25 (0.69–2.27)	1.10 (0.61–2.01)	58(0.05)	200(0.05)	1.10 (0.75–1.62)	1.02 (0.69–1.50)
SSAD								
Never	186802 (98.0)	750522 (98.4)	(reference)	(reference)	105325 (96.3)	393263 (96.7)	(reference)	(reference)
Mild	2560 (1.3)	8185 (1.1)	1.26 (1.19–1.34)	1.23 (1.16–1.31)	3290(3.01)	11423(2.81)	1.09 (1.04–1.15)	1.08 (1.02–1.14)
Moderate	1175 (0.6)	3581 (0.5)	1.32 (1.21–1.44)	1.26 (1.15–1.37)	694(0.63)	2058(0.51)	1.29 (1.15–1.44)	1.25 (1.12–1.41)
Severe	96 (0.1)	268 (0.0)	1.44 (1.06–1.96)	1.37 (1.00–1.87)	18(0.02)	53(0.01)	1.25 (0.62–2.55)	1.23 (0.60–2.50)
Very severe	38 (0.0)	128 (0.0)	1.19 (0.74–1.92)	1.11 (0.69–1.80)	4(0.00)	18(0.00)	0.79 (0.19–3.31)	0.80 (0.19–3.35)

Abbreviations: CI = confidence interval; SSAD = severe stress and adjustment disorder

*Definition of severity was as follows based on records within the past 90 days: very severe (requiring inpatient admission), severe (written prescription for an antidepressant), moderate (requiring referral from general practice to a mental health service in the UK; remaining Danish patients) or mild (remaining UK patients).

†Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

Table e6. Odds ratios (99% confidence intervals) for the association between mood disorders and herpes zoster, by timing using different cutoffs between 'current' and 'recent' mood disorder.

	Denmark					The UK				
	7 days	**14 days**	**30 days**	**90 days**	**180 days**	**7 days**	**14 days**	**30 days**	**90 days**	**180 days**
Any mood disorder										
Never	(reference)	(reference)	(reference)	**(reference)**	(reference)	(reference)	(reference)	(reference)	**(reference)**	(reference)
Ever	1.15 (1.12–1.19)	1.15 (1.12–1.19)	1.15 (1.12–1.19)	**1.15 (1.12–1.19)**	1.15 (1.12–1.19)	1.12 (1.11–1.14)	1.12 (1.11–1.14)	1.12 (1.11–1.14)	**1.12 (1.11–1.14)**	1.12 (1.11–1.14)
Current	1.11 (0.75–1.65)	1.11 (0.83–1.48)	1.10 (0.90–1.34)	**1.18 (1.04–1.34)**	1.22 (1.12–1.34)	1.14 (0.97–1.33)	1.19 (1.07–1.33)	1.19 (1.10–1.29)	**1.18 (1.13–1.24)**	1.18 (1.14–1.23)
Recent	1.20 (1.12–1.28)	1.20 (1.12–1.29)	1.21 (1.12–1.30)	**1.20 (1.10–1.31)**	1.16 (1.04–1.28)	1.19 (1.16–1.23)	1.19 (1.16–1.23)	1.19 (1.16–1.23)	**1.20 (1.15–1.24)**	1.20 (1.15–1.26)
Former	1.15 (1.12–1.18)	1.15 (1.12–1.18)	1.15 (1.12–1.18)	**1.15 (1.12–1.18)**	1.15 (1.12–1.18)	1.11 (1.09–1.13)	1.11 (1.09–1.13)	1.11 (1.09–1.13)	**1.11 (1.09–1.13)**	1.11 (1.09–1.13)
Depression										
Never	(reference)	(reference)	(reference)	**(reference)**	(reference)	(reference)	(reference)	(reference)	**(reference)**	(reference)
Ever	1.11 (1.07–1.14)	1.11 (1.07–1.14)	1.11 (1.07–1.14)	**1.11 (1.07–1.14)**	1.11 (1.07–1.14)	1.12 (1.10–1.13)	1.12 (1.10–1.13)	1.12 (1.10–1.13)	**1.12 (1.10–1.13)**	1.12 (1.10–1.13)
Current	1.01 (0.62–1.64)	0.91 (0.63–1.32)	0.98 (0.77–1.26)	**1.09 (0.93–1.26)**	1.15 (1.03–1.29)	1.14 (0.94–1.38)	1.17 (1.03–1.34)	1.17 (1.07–1.29)	**1.15 (1.08–1.22)**	1.15 (1.10–1.21)
Recent	1.14 (1.04–1.24)	1.15 (1.05–1.25)	1.15 (1.06–1.26)	**1.15 (1.04–1.27)**	1.11 (0.98–1.26)	1.17 (1.13–1.21)	1.16 (1.12–1.21)	1.16 (1.12–1.21)	**1.17 (1.13–1.22)**	1.18 (1.12–1.24)
Former	1.10 (1.07–1.14)	1.10 (1.07–1.14)	1.10 (1.07–1.14)	**1.10 (1.07–1.14)**	1.10 (1.07–1.14)	1.10 (1.08–1.12)	1.10 (1.08–1.12)	1.10 (1.08–1.12)	**1.10 (1.08–1.12)**	1.10 (1.08–1.12)
Anxiety										
Never	(reference)	(reference)	(reference)	**(reference)**	(reference)	(reference)	(reference)	(reference)	**(reference)**	(reference)
Ever	1.23 (1.17–1.30)	1.23 (1.17–1.30)	1.23 (1.17–1.30)	**1.23 (1.17–1.30)**	1.23 (1.17–1.30)	1.12 (1.10–1.14)	1.12 (1.10–1.14)	1.12 (1.10–1.14)	**1.12 (1.10–1.14)**	1.12 (1.10–1.14)
Current	1.14 (0.43–3.06)	1.28 (0.65–2.51)	1.52 (0.94–2.48)	**1.51 (1.10–2.06)**	1.41 (1.12–1.78)	1.09 (0.82–1.44)	1.19 (0.97–1.45)	1.18 (1.02–1.36)	**1.22 (1.12–1.33)**	1.21 (1.13–1.29)
Recent	1.33 (1.11–1.59)	1.33 (1.10–1.59)	1.29 (1.07–1.57)	**1.25 (1.01–1.55)**	1.21 (0.92–1.59)	1.21 (1.15–1.27)	1.21 (1.15–1.27)	1.21 (1.15–1.28)	**1.20 (1.13–1.28)**	1.21 (1.12–1.30)
Former	1.22 (1.16–1.30)	1.22 (1.16–1.30)	1.22 (1.16–1.30)	**1.22 (1.16–1.30)**	1.22 (1.16–1.30)	1.10 (1.08–1.13)	1.10 (1.08–1.13)	1.10 (1.08–1.13)	**1.10 (1.08–1.13)**	1.10 (1.08–1.13)
SSAD										
Never	(reference)	(reference)	(reference)	**(reference)**	(reference)	(reference)	(reference)	(reference)	**(reference)**	(reference)
Ever	1.24 (1.18–1.30)	1.24 (1.18–1.30)	1.24 (1.18–1.30)	**1.24 (1.18–1.30)**	1.24 (1.18–1.30)	1.14 (1.10–1.19)	1.14 (1.10–1.19)	1.14 (1.10–1.19)	**1.14 (1.10–1.19)**	1.14 (1.10–1.19)
Current	1.78 (0.77–4.09)	1.81 (1.04–3.17)	1.27 (0.84–1.93)	**1.29 (0.99–1.67)**	1.40 (1.16–1.69)	0.96 (0.31–2.92)	1.26 (0.62–2.56)	1.10 (0.65–1.85)	**1.16 (0.88–1.54)**	1.14 (0.93–1.39)
Recent	1.37 (1.19–1.58)	1.36 (1.18–1.57)	1.40 (1.21–1.62)	**1.42 (1.21–1.67)**	1.37 (1.12–1.67)	1.25 (1.08–1.43)	1.24 (1.08–1.43)	1.25 (1.08–1.44)	**1.27 (1.08–1.48)**	1.34 (1.11–1.62)
Former	1.22 (1.16–1.29)	1.22 (1.16–1.29)	1.22 (1.16–1.29)	**1.22 (1.16–1.29)**	1.22 (1.16–1.29)	1.14 (1.09–1.18)	1.14 (1.09–1.18)	1.14 (1.09–1.18)	**1.14 (1.09–1.18)**	1.14 (1.09–1.18)

Abbreviations: CI = confidence interval; SSAD = severe stress and adjustment disorder

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

†Main definition

Table e7. Odds ratios for the association between mood disorders and herpes zoster, sensitivity analysis excluding those with only possible or unspecific prior diagnoses.

	Denmark		UK	
	Unadjusted odds ratio (99% CI)	**Adjusted odds ratio (99% CI)***	**Unadjusted odds ratio (99% CI)**	**Adjusted odds ratio (99% CI)***
Depression				
Timing				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.15 (1.11–1.19)	1.11 (1.08–1.15)	1.15 (1.13–1.17)	1.12 (1.10–1.14)
Current	1.16 (1.00–1.36)	1.09 (0.93–1.27)	1.19 (1.12–1.26)	1.15 (1.09–1.22)
Recent	1.23 (1.11–1.36)	1.16 (1.05–1.29)	1.22 (1.17–1.28)	1.18 (1.13–1.23)
Former	1.14 (1.10–1.18)	1.11 (1.07–1.15)	1.13 (1.11–1.15)	1.11 (1.08–1.13)
Severity				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.15 (1.11–1.19)	1.11 (1.08–1.15)	1.14 (1.11–1.16)	1.11 (1.09–1.13)
Moderate	1.25 (1.01–1.54)	1.18 (0.95–1.46)	1.18 (0.91–1.54)	1.14 (0.88–1.49)
Severe	1.07 (0.86–1.33)	0.99 (0.80–1.24)	1.05 (0.81–1.37)	0.94 (0.72–1.23)
Anxiety				
Timing				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.28 (1.21–1.35)	1.23 (1.17–1.30)	1.13 (1.10–1.16)	1.11 (1.08–1.14)
Current	1.83 (1.35–2.49)	1.53 (1.12–2.09)	1.25 (1.12–1.38)	1.22 (1.10–1.35)
Recent	1.36 (1.10–1.68)	1.25 (1.01–1.55)	1.23 (1.14–1.32)	1.20 (1.12–1.29)
Former	1.26 (1.19–1.34)	1.22 (1.16–1.30)	1.11 (1.08–1.14)	1.10 (1.07–1.13)
Severity				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.27 (1.20–1.34)	1.23 (1.16–1.30)	1.12 (1.09–1.16)	1.10 (1.07–1.14)
Moderate	2.15 (1.49–3.08)	1.75 (1.21–2.54)	1.28 (0.89–1.85)	1.24 (0.86–1.79)
Severe	1.25 (0.69–2.27)	1.10 (0.61–2.01)	1.09 (0.74–1.61)	1.01 (0.69–1.49)

Abbreviations: CI = confidence interval

All diagnosis codes included for severe stress and adjustment disorder were considered definite.

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

Table e8. Odds ratios for the association between mood disorders and herpes zoster, by timing. Sensitivity analysis considering each mood disorder exclusively (*i.e.*, including no persons with codes for more than one subtype of mood disorder).

	Denmark		The UK	
	Unadjusted odds ratio (99% CI)	**Adjusted odds ratio (99% CI)***	**Unadjusted odds ratio (99% CI)**	**Adjusted odds ratio (99% CI)***
Depression				
Timing				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.12 (1.08–1.16)	1.08 (1.05–1.12)	1.13 (1.11–1.15)	1.10 (1.08–1.13)
Current	1.11 (0.93–1.32)	1.05 (0.88–1.25)	1.17 (1.09–1.26)	1.14 (1.05–1.23)
Recent	1.18 (1.06–1.33)	1.12 (1.00–1.25)	1.19 (1.13–1.26)	1.15 (1.09–1.21)
Former	1.11 (1.07–1.15)	1.08 (1.04–1.12)	1.12 (1.09–1.14)	1.09 (1.07–1.12)
Severity				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.12 (1.08–1.16)	1.09 (1.05–1.13)	1.13 (1.10–1.16)	1.10 (1.07–1.13)
Moderate	1.17 (0.93–1.49)	1.14 (0.90–1.45)	1.22 (0.84–1.76)	1.18 (0.82–1.71)
Severe	1.02 (0.79–1.31)	0.93 (0.72–1.20)	1.08 (0.74–1.59)	0.98 (0.66–1.43)
Anxiety				
Timing				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.28 (1.21–1.36)	1.23 (1.16–1.31)	1.15 (1.13–1.17)	1.13 (1.10–1.15)
Current	2.01 (1.44–2.80)	1.67 (1.18–2.34)	1.26 (1.15–1.39)	1.22 (1.11–1.34)
Recent	1.35 (1.06–1.73)	1.24 (0.96–1.59)	1.24 (1.16–1.32)	1.21 (1.14–1.29)
Former	1.26 (1.18–1.34)	1.22 (1.15–1.30)	1.14 (1.11–1.16)	1.12 (1.09–1.14)
Severity				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.26 (1.19–1.34)	1.22 (1.15–1.30)	1.14 (1.11–1.17)	1.12 (1.09–1.15)
Moderate	2.22 (1.51–3.28)	1.81 (1.21–2.70)	1.30 (0.92–1.84)	1.26 (0.89–1.79)
Severe	1.54 (0.81–2.93)	1.35 (0.70–2.61)	1.18 (0.79–1.75)	1.08 (0.73–1.61)
SSAD				
Timing				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.29 (1.23–1.35)	1.25 (1.19–1.31)	1.21 (1.16–1.26)	1.19 (1.14–1.23)
Current	1.37 (1.06–1.77)	1.29 (1.00–1.68)	1.25 (0.94–1.65)	1.21 (0.91–1.60)
Recent	1.49 (1.27–1.75)	1.43 (1.22–1.68)	1.33 (1.14–1.56)	1.31 (1.12–1.54)
Former	1.27 (1.20–1.34)	1.23 (1.17–1.30)	1.20 (1.16–1.25)	1.18 (1.14–1.23)
Severity				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.29 (1.22–1.35)	1.25 (1.19–1.31)	1.17 (1.11–1.23)	1.15 (1.09–1.20)
Moderate	1.45 (1.07–1.97)	1.38 (1.01–1.88)	1.32 (0.65–2.67)	1.27 (0.62–2.60)
Severe	1.20 (0.75–1.93)	1.12 (0.69–1.81)	0.82 (0.20–3.45)	0.83 (0.20–3.46)

Abbreviations: CI = confidence interval; SSAD = severe stress and adjustment disorder

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

Table e9. Sensitivity analysis excluding strata where herpes zoster cases were included based on prescriptions without herpes zoster stated specifically as the indication (Danish data).

	Main analysis	Restricting to those with indication codes explicitly stating herpes zoster
Any		
Timing		
Never	(reference)	(reference)
Ever	1.15 (1.12–1.19)	1.13 (1.09–1.18)
Current	1.18 (1.04–1.34)	1.22 (1.01–1.48)
Recent	1.20 (1.10–1.31)	1.16 (1.02–1.32)
Former	1.15 (1.12–1.18)	1.13 (1.08–1.18)
Severity		
Never	(reference)	(reference)
Mild	1.15 (1.12–1.18)	1.13 (1.08–1.18)
Moderate	1.28 (1.09–1.51)	1.32 (1.03–1.69)
Severe	1.05 (0.87–1.27)	1.11 (0.84–1.48)
Depression		
Timing		
Never	(reference)	(reference)
Ever	1.11 (1.07–1.14)	1.10 (1.05–1.15)
Current	1.09 (0.93–1.26)	1.15 (0.92–1.44)
Recent	1.15 (1.04–1.27)	1.14 (0.99–1.33)
Former	1.10 (1.07–1.14)	1.09 (1.04–1.15)
Severity		
Never	(reference)	(reference)
Mild	1.11 (1.07–1.14)	1.10 (1.04–1.15)
Moderate	1.16 (0.95–1.43)	1.26 (0.92–1.72)
Severe	0.99 (0.80–1.23)	1.05 (0.76–1.44)
Anxiety		
Timing		
Never	(reference)	(reference)
Ever	1.23 (1.17–1.30)	1.21 (1.11–1.31)
Current	1.51 (1.10–2.06)	1.52 (0.96–2.42)
Recent	1.25 (1.01–1.55)	1.15 (0.82–1.62)
Former	1.22 (1.16–1.30)	1.20 (1.10–1.31)
Severity		
Never		
Mild	1.22 (1.16–1.29)	1.20 (1.10–1.30)
Moderate	1.71 (1.18–2.48)	1.70 (0.97–2.98)
Severe	1.10 (0.61–2.01)	1.21 (0.52–2.79)
SSAD		
Timing		
Never	(reference)	(reference)
Ever	1.24 (1.18–1.30)	1.16 (1.08–1.25)
Current	1.29 (0.99–1.67)	1.35 (0.91–2.01)
Recent	1.42 (1.21–1.67)	1.29 (0.98–1.69)
Former	1.22 (1.16–1.29)	1.15 (1.06–1.24)
Severity		
Never	(reference)	(reference)
Mild	1.24 (1.18–1.30)	1.16 (1.07–1.25)
Moderate	1.37 (1.01–1.87)	1.45 (0.92–2.30)
Severe	1.11 (0.69–1.80)	1.11 (0.50–2.45)

Abbreviations: CI = confidence interval; SSAD = severe stress and adjustment disorder

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

Table e10. Odds ratios (99% confidence intervals) for the association between mood disorders and herpes zoster. Sensitivity analysis adjusting excluding case-control strata with persons included after marketing of Zostavax in the UK

	Main analysis*	Excluding strata after Aug 31, 2013
Any		
Timing		
Never	(reference)	(reference)
Ever	1.12 (1.11–1.14)	1.13 (1.11–1.14)
Current	1.18 (1.13–1.24)	1.19 (1.13–1.25)
Recent	1.20 (1.15–1.24)	1.20 (1.16–1.24)
Former	1.11 (1.09–1.13)	1.11 (1.09–1.13)
Severity		
Mild	1.11 (1.09–1.14)	1.12 (1.09–1.14)
Moderate	1.24 (0.98–1.58)	1.24 (0.97–1.58)
Severe	1.00 (0.80–1.25)	0.98 (0.78–1.23)
Depression		
Timing		
Never	(reference)	(reference)
Ever	1.12 (1.10–1.13)	1.12 (1.10–1.14)
Current	1.15 (1.08–1.22)	1.15 (1.08–1.22)
Recent	1.17 (1.13–1.22)	1.18 (1.13–1.23)
Former	1.10 (1.08–1.12)	1.10 (1.08–1.13)
Severity		
Never	(reference)	(reference)
Mild	1.11 (1.08–1.13)	1.11 (1.09–1.14)
Moderate	1.18 (0.91–1.52)	1.18 (0.91–1.53)
Severe	0.94 (0.72–1.23)	0.94 (0.72–1.24)
Anxiety		
Timing		
Never	(reference)	(reference)
Ever	1.12 (1.10–1.14)	1.12 (1.10–1.14)
Current	1.22 (1.12–1.33)	1.23 (1.12–1.34)
Recent	1.20 (1.13–1.28)	1.20 (1.13–1.28)
Former	1.10 (1.08–1.13)	1.11 (1.08–1.13)
Severity		
Never	(reference)	(reference)
Mild	1.10 (1.07–1.13)	1.11 (1.08–1.14)
Moderate	1.23 (0.89–1.70)	1.24 (0.89–1.72)
Severe	1.02 (0.69–1.50)	0.95 (0.63–1.42)
SSAD		
Timing		
Never	(reference)	(reference)
Ever	1.14 (1.10–1.19)	1.15 (1.10–1.19)
Current	1.16 (0.88–1.54)	1.17 (0.88–1.55)
Recent	1.27 (1.08–1.48)	1.26 (1.07–1.48)
Former	1.14 (1.09–1.18)	1.14 (1.10–1.19)
Severity		
Never	(reference)	(reference)
Mild	1.11 (1.05–1.16)	1.11 (1.05–1.16)
Moderate	1.22 (0.60–2.50)	1.17 (0.57–2.44)
Severe	0.80 (0.19–3.34)	0.80 (0.19–3.34)

Abbreviations: CI = confidence interval; SSAD = severe stress and adjustment disorder
*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.
†Vaccine was not available in Denmark during the study period

Table e11. Distribution of individual-level socioeconomic status and lifestyle factors among herpes zoster cases and matched controls.

	Cases n (%)	Controls n (%)
Denmark		
Highest achieved education		
Long (>15 years)	33,006 (17.3)	121,098 (15.9)
Medium (>10–15 years)	72,508 (38.0)	295,076 (38.7)
Short (≤10 years)	66,494 (34.9)	269,752 (35.4)
Missing	18,663 (9.8)	76,758 (10.1)
UK		
Quintiles of individual-level Index of Multiple Deprivation score		
1 (least deprived)	27,305 (15.4)	103,593 (15.4)
2	27,068 (15.3)	103,060 (15.3)
3	22,672 (12.8)	86,407 (12.8)
4	18,621 (10.5)	70,840 (10.5)
5 (most deprived)	13,659 (7.7)	51,556 (7.6)
Missing	68,036 (38.4)	259,047 (38.4)
Body mass index category		
Underweight	3,465 (2.0)	13,034 (1.9)
Normal weight	61,490 (34.7)	230,651 (34.2)
Overweight	59,192 (33.4)	220,710 (32.7)
Obese	37,624 (21.2)	139,790 (20.7)
Missing	15,590 (8.8)	70,318 (10.4)
Smoking status		
Non-smoker	66,989 (37.8)	255,530 (37.9)
Current smoker	42,279 (23.8)	167,279 (24.8)
Ex-smoker	66,427 (37.5)	238,809 (35.4)
Missing	1,666 (0.9)	12,885 (1.9)
Alcohol use		
Non-drinker	17,248 (9.7)	67,747 (10.0)
Current drinker	127,004 (71.6)	474,380 (70.3)
Ex-drinker	16,724 (9.4)	60,328 (8.9)
Missing	16,385 (9.2)	72,048 (10.68)

Table e12. Odds ratios (99% confidence intervals) for the association between mood disorders and herpes zoster. Sensitivity analysis adjusting additionally for individual-level socioeconomic status and lifestyle factors (UK only).

	Denmark		The UK		
	Main analysis*	**Adjusted additionally for educational attainment†**	**Main analysis***	**Adjusted additionally for individual-level IMD†**	**Adjusted additionally for lifestyle factors‡**
Any					
Timing					
Never	(reference)	(reference)	(reference)	(reference)	(reference)
Ever	1.15 (1.12–1.19)	1.16 (1.13–1.19)	1.12 (1.11–1.14)	1.12 (1.09–1.14)	1.12 (1.10–1.14)
Current	1.18 (1.04–1.34)	1.18 (1.03–1.35)	1.18 (1.13–1.24)	1.15 (1.08–1.23)	1.17 (1.11–1.24)
Recent	1.20 (1.10–1.31)	1.22 (1.11–1.34)	1.20 (1.15–1.24)	1.19 (1.14–1.25)	1.18 (1.13–1.22)
Former	1.15 (1.12–1.18)	1.15 (1.12–1.19)	1.11 (1.09–1.13)	1.10 (1.08–1.12)	1.10 (1.08–1.12)
Severity					
Never	(reference)	(reference)		(reference)	
Mild	1.15 (1.12–1.18)	1.16 (1.13–1.19)	1.11 (1.09–1.14)	1.12 (1.09–1.14)	1.10 (1.08–1.13)
Moderate	1.28 (1.09–1.51)	1.31 (1.10–1.56)	1.24 (0.98–1.58)	1.26 (0.99–1.60)	1.24 (0.96–1.62)
Severe	1.05 (0.87–1.27)	1.02 (0.83–1.26)	1.00 (0.80–1.25)	1.00 (0.80–1.25)	0.99 (0.77–1.26)
Depression					
Timing					
Never	(reference)	(reference)	(reference)	(reference)	(reference)
Ever	1.11 (1.07–1.14)	1.11 (1.07–1.14)	1.12 (1.10–1.13)	1.11 (1.09–1.13)	1.11 (1.09–1.13)
Current	1.09 (0.93–1.26)	1.06 (0.90–1.25)	1.15 (1.08–1.22)	1.12 (1.04–1.21)	1.14 (1.07–1.22)
Recent	1.15 (1.04–1.27)	1.16 (1.04–1.29)	1.17 (1.13–1.22)	1.16 (1.10–1.23)	1.15 (1.10–1.20)
Former	1.10 (1.07–1.14)	1.10 (1.06–1.14)	1.10 (1.08–1.12)	1.10 (1.08–1.13)	1.10 (1.08–1.12)
Severity					
Never	(reference)	(reference)	(reference)	(reference)	(reference)
Mild	1.11 (1.07–1.14)	1.11 (1.07–1.15)	1.11 (1.08–1.13)	1.11 (1.09–1.13)	1.10 (1.07–1.13)
Moderate	1.16 (0.95–1.43)	1.16 (0.93–1.46)	1.18 (0.91–1.52)	1.19 (0.92–1.54)	1.17 (0.88–1.55)
Severe	0.99 (0.80–1.23)	0.96 (0.75–1.22)	0.94 (0.72–1.23)	0.94 (0.72–1.23)	0.93 (0.69–1.24)
Anxiety					
Timing					
Never	(reference)		(reference)		(reference)
Ever	1.23 (1.17–1.30)	1.25 (1.18–1.32)	1.12 (1.10–1.14)	1.10 (1.08–1.13)	1.11 (1.09–1.14)
Current	1.51 (1.10–2.06)	1.55 (1.12–2.15)	1.22 (1.12–1.33)	1.19 (1.06–1.33)	1.18 (1.07–1.30)
Recent	1.25 (1.01–1.55)	1.23 (0.98–1.54)	1.20 (1.13–1.28)	1.21 (1.12–1.31)	1.20 (1.13–1.28)
Former	1.22 (1.16–1.30)	1.24 (1.17–1.32)	1.10 (1.08–1.13)	1.09 (1.06–1.12)	1.10 (1.07–1.12)
Severity					
Never		(reference)	(reference)	(reference)	(reference)
Mild	1.22 (1.16–1.29)	1.24 (1.17–1.32)	1.10 (1.07–1.13)	1.10 (1.08–1.13)	1.09 (1.06–1.12)
Moderate	1.71 (1.18–2.48)	1.83 (1.24–2.69)	1.23 (0.89–1.70)	1.26 (0.91–1.74)	1.24 (0.88–1.76)
Severe	1.10 (0.61–2.01)	1.06 (0.57–1.99)	1.02 (0.69–1.50)	1.02 (0.69–1.50)	1.00 (0.66–1.52)
SSAD					
Timing					
Never	(reference)	(reference)	(reference)	(reference)	(reference)
Ever	1.24 (1.18–1.30)	1.25 (1.19–1.32)	1.14 (1.10–1.19)	1.11 (1.05–1.16)	1.13 (1.09–1.18)
Current	1.29 (0.99–1.67)	1.29 (0.98–1.68)	1.16 (0.88–1.54)	1.02 (0.69–1.49)	1.18 (0.87–1.59)
Recent	1.42 (1.21–1.67)	1.44 (1.22–1.70)	1.27 (1.08–1.48)	1.32 (1.08–1.62)	1.20 (1.01–1.43)
Former	1.22 (1.16–1.29)	1.24 (1.17–1.30)	1.14 (1.09–1.18)	1.10 (1.04–1.15)	1.13 (1.09–1.18)
Severity					
Never	(reference)	(reference)	(reference)	(reference)	(reference)
Mild	1.24 (1.18–1.30)	1.25 (1.19–1.32)	1.11 (1.05–1.16)	1.11 (1.05–1.16)	1.09 (1.03–1.15)
Moderate	1.37 (1.01–1.87)	1.38 (1.00–1.90)	1.22 (0.60–2.50)	1.22 (0.60–2.50)	1.00 (0.46–2.19)
Severe	1.11 (0.69–1.80)	1.10 (0.68–1.80)	0.80 (0.19–3.34)	0.80 (0.19–3.35)	0.49 (0.07–3.63)

Abbreviations: CI = confidence interval; IMD=Index of Multiple Deprivation; SSAD = severe stress and adjustment disorder

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

†Adjusted additionally highest achieved education in Denmark and quintiles of IMD scores in the UK.

‡Adjusted additionally for body mass index category (underweight, normal weight, overweight, obese), smoking status (non–smoker, current smoker, ex-smoker), and alcohol use (non-drinker, current drinker, ex-drinker). Data on lifestyle factors were not available in the Danish data.

Table e13. Odds ratios for the association between mood disorders and herpes zoster. *Post hoc* analysis including secondary hospital diagnoses of herpes zoster.

	Denmark		The UK	
	Unadjusted odds ratio (99% CI)	**Adjusted odds ratio (99% CI)***	**Unadjusted odds ratio (99% CI)**	**Adjusted odds ratio (99% CI)***
Any				
Timing				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.20 (1.17–1.23)	1.16 (1.13–1.19)	1.20 (1.18–1.21)	1.17 (1.15–1.19)
Current	1.29 (1.14–1.46)	1.19 (1.05–1.34)	1.33 (1.26–1.39)	1.27 (1.21–1.34)
– First-time	1.37 (1.16–1.61)	1.25 (1.06–1.47)	1.26 (1.16–1.38)	1.22 (1.12–1.33)
– Not first-time	1.20 (1.01–1.44)	1.12 (0.93–1.34)	1.36 (1.28–1.44)	1.30 (1.23–1.38)
Recent	1.30 (1.19–1.41)	1.23 (1.13–1.33)	1.30 (1.25–1.35)	1.25 (1.21–1.30)
Former	1.18 (1.15–1.22)	1.15 (1.12–1.18)	1.17 (1.15–1.19)	1.15 (1.13–1.17)
Severity				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.19 (1.16–1.23)	1.16 (1.13–1.19)	1.18 (1.16–1.20)	1.15 (1.13–1.17)
Moderate	1.33 (1.14–1.56)	1.23 (1.04–1.44)	1.47 (1.16–1.87)	1.42 (1.12–1.80)
Severe	1.22 (1.02–1.47)	1.12 (0.93–1.35)	1.31 (1.06–1.61)	1.16 (0.94–1.43)
Depression				
Timing				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.15 (1.11–1.18)	1.11 (1.08–1.15)	1.19 (1.17–1.21)	1.16 (1.14–1.18)
Current	1.17 (1.01–1.35)	1.09 (0.94–1.26)	1.29 (1.22–1.37)	1.24 (1.17–1.31)
– First-time	1.22 (0.99–1.51)	1.14 (0.91–1.41)	1.22 (1.09–1.36)	1.17 (1.05–1.31)
– Not first-time	1.13 (0.92–1.38)	1.05 (0.85–1.28)	1.32 (1.23–1.41)	1.26 (1.18–1.35)
Recent	1.26 (1.15–1.39)	1.20 (1.09–1.32)	1.30 (1.24–1.35)	1.24 (1.19–1.29)
Former	1.14 (1.10–1.17)	1.10 (1.07–1.14)	1.17 (1.15–1.19)	1.14 (1.12–1.16)
Severity				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.15 (1.11–1.18)	1.11 (1.08–1.15)	1.18 (1.15–1.20)	1.15 (1.12–1.17)
Moderate	1.20 (0.98–1.47)	1.12 (0.92–1.38)	1.38 (1.07–1.78)	1.32 (1.02–1.71)
Severe	1.13 (0.92–1.39)	1.04 (0.85–1.29)	1.25 (0.98–1.60)	1.09 (0.85–1.40)
Anxiety				
Timing				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.27 (1.21–1.34)	1.23 (1.16–1.29)	1.17 (1.15–1.19)	1.15 (1.13–1.17)
Current	1.88 (1.39–2.56)	1.62 (1.18–2.22)	1.33 (1.22–1.45)	1.30 (1.19–1.42)
– First-time	2.14 (1.47–3.12)	1.75 (1.19–2.57)	1.29 (1.11–1.49)	1.26 (1.09–1.45)
– Not first-time	1.48 (0.87–2.52)	1.41 (0.82–2.42)	1.36 (1.22–1.52)	1.33 (1.19–1.48)
Recent	1.43 (1.16–1.76)	1.34 (1.08–1.66)	1.26 (1.18–1.33)	1.22 (1.15–1.30)
Former	1.25 (1.18–1.32)	1.21 (1.14–1.28)	1.15 (1.13–1.18)	1.13 (1.11–1.16)
Severity				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.26 (1.19–1.33)	1.22 (1.15–1.28)	1.15 (1.12–1.18)	1.13 (1.10–1.16)
Moderate	1.99 (1.39–2.84)	1.69 (1.17–2.44)	1.54 (1.11–2.14)	1.48 (1.06–2.06)
Severe	1.65 (0.91–2.97)	1.45 (0.79–2.66)	1.31 (0.90–1.90)	1.18 (0.81–1.72)
SSAD				
Timing				
Never	(reference)	(reference)	(reference)	(reference)
Ever	1.30 (1.23–1.36)	1.25 (1.19–1.31)	1.19 (1.15–1.24)	1.17 (1.13–1.22)
Current	1.30 (1.01–1.68)	1.22 (0.95–1.58)	1.15 (0.87–1.51)	1.13 (0.86–1.49)
– First-time	1.15 (0.83–1.60)	1.07 (0.77–1.49)	1.11 (0.80–1.53)	1.08 (0.78–1.50)
– Not first-time	1.59 (1.06–2.37)	1.52 (1.01–2.28)	1.27 (0.76–2.12)	1.27 (0.76–2.12)
Recent	1.40 (1.20–1.64)	1.32 (1.13–1.55)	1.31 (1.12–1.54)	1.30 (1.11–1.52)
Former	1.28 (1.22–1.35)	1.24 (1.18–1.31)	1.18 (1.14–1.23)	1.17 (1.12–1.21)
Severity				
Never	(reference)	(reference)	(reference)	(reference)
Mild	1.29 (1.23–1.36)	1.25 (1.19–1.31)	1.16 (1.10–1.21)	1.14 (1.09–1.20)
Moderate	1.35 (1.00–1.83)	1.27 (0.93–1.72)	1.17 (0.59–2.34)	1.12 (0.56–2.25)
Severe	1.20 (0.75–1.90)	1.13 (0.71–1.81)	1.70 (0.36–8.02)	1.76 (0.37–8.34)

Abbreviations: CI = confidence interval; SSAD = severe stress and adjustment disorder

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, asthma, chronic kidney disease, diabetes, inhaled corticosteroids, solid organ transplantation, HIV infection, leukemia, lymphoma, myeloma, hematopoietic stem cell/bone marrow transplantation, other unspecified cellular immune deficiencies, oral glucocorticoids, and other immunosuppressive treatment.

Table e14. Odds ratios for the association between mood disorders and herpes zoster in Denmark, including antidepressants users in the definition of mood disorder to capture patients treated in outside the hospital-based setting. *Post hoc* analysis including secondary hospital diagnoses of herpes zoster.

	Unadjusted odds ratio (99% CI)	Adjusted odds ratio (99% CI)*
Timing		
Never	(reference)	(reference)
Ever	1.31 (1.29-1.33)	1.26 (1.24-1.28)
Current	1.33 (1.30-1.36)	1.26 (1.23-1.29)
– First-time	1.41 (1.28-1.56)	1.29 (1.17-1.43)
– Not first-time	1.32 (1.29-1.35)	1.26 (1.23-1.29)
Recent	1.37 (1.32-1.41)	1.31 (1.26-1.35)
Former	1.28 (1.26-1.31)	1.25 (1.22-1.27)
Severity		
Never	(reference)	(reference)
Mild	1.30 (1.28-1.33)	1.26 (1.24-1.28)
Moderate	1.32 (1.29-1.36)	1.26 (1.23-1.29)
Severe	1.41 (1.21-1.66)	1.29 (1.10-1.52)
Very severe	1.29 (1.08-1.55)	1.19 (0.98-1.43)

Abbreviations: CI = confidence interval

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

Table e15. Odds ratios for the association between any current mood disorders and herpes zoster, subgroup analysis. *Post hoc* analysis including secondary hospital diagnoses of herpes zoster.

	Denmark		The UK	
	Unadjusted odds ratio (99% CI)	**Adjusted odds ratio (99% CI)***	**Unadjusted odds ratio (99% CI)**	**Adjusted odds ratio (99% CI)***
Main definition of mood disorders				
Sex				
Female	1.42 (1.22-1.64)	1.34 (1.15-1.56)	1.33 (1.26-1.41)	1.29 (1.22-1.36)
Male	1.08 (0.88-1.34)	0.93 (0.75-1.16)	1.32 (1.20-1.45)	1.25 (1.13-1.37)
Age, years				
<50	1.42 (1.09-1.86)	1.31 (0.99-1.72)	1.49 (1.37-1.61)	1.44 (1.32-1.56)
50–59	1.18 (0.88-1.56)	1.05 (0.78-1.40)	1.36 (1.23-1.51)	1.31 (1.18-1.46)
60–69	1.52 (1.14-2.02)	1.34 (1.00-1.79)	1.29 (1.15-1.45)	1.22 (1.08-1.37)
≥70	1.20 (1.00-1.44)	1.13 (0.94-1.36)	1.15 (1.04-1.27)	1.10 (1.00-1.21)
Including also antidepressants as proxy for mood disorder in Denmark				
Sex				
Female	1.60 (1.56-1.65)	1.55 (1.50-1.59)	–	–
Male	0.92 (0.89-0.96)	0.85 (0.81-0.89)	–	–
Age, years				
<50	1.61 (1.51-1.71)	1.53 (1.44-1.63)	–	–
50–59	1.41 (1.33-1.49)	1.33 (1.26-1.41)	–	–
60–69	1.32 (1.25-1.39)	1.22 (1.16-1.29)	–	–
≥70	1.22 (1.18-1.26)	1.17 (1.13-1.21)	–	–

Abbreviations: CI = confidence interval

*Adjusted for rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes, chronic kidney disease, HIV infection, hematopoietic stem cell/bone marrow transplantation, solid organ transplantation, other cellular immune deficiency, leukemia, lymphoma, myeloma, oral glucocorticoids, other immunosuppressant drugs, and inhaled glucocorticoids.

- **Appendix IV**:

Paper IV

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REVIEW

Herpes zoster as a marker of occult cancer: A systematic review and meta-analysis

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Summary *Objectives:* Researchers have advocated for an increased awareness of occult cancer among herpes zoster patients, but there are no systematic reviews to support these claims. We therefore conducted a systematic review and meta-analysis of evidence on zoster and risk of occult cancer.
Methods: Through February 18, 2016, we searched PubMed, EMBASE and references of relevant papers for studies on zoster and risk of any cancer. One author screened retrieved papers by title and abstract; included papers were reviewed by two authors for eligibility, data extraction, and potential biases. Despite statistical heterogeneity, associations were consistently in the same direction and we therefore computed pooled relative risks using random-effects models.
Results: We identified 46 eligible studies, 10 of which considered all cancer types combined. The pooled relative risk for any cancer was 1.42 (95% confidence interval: 1.18, 1.71) overall and 1.83 (95% confidence interval: 1.17, 2.87) at one year after zoster. Considering cancer subtypes, the highest estimates were generally reported for occult hematological cancer. The absolute risk of any cancer at one year after presentation with zoster was 0.7—1.8%.
Conclusion: This study supports an association between zoster and occult cancer, but the low absolute risk of cancer limits the clinical implications.

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Introduction

Herpes zoster is characterized by a unilateral vesicular rash that is accompanied by severe neuralgia.[1,2] It is caused by reactivation of the varicella-zoster virus, which lies dormant in the sensory ganglia following the primary infection, chickenpox.[1,2] The risk of reactivation increases with age and it is estimated that up to 50% of people who live up to 85 years will develop herpes zoster.[1]

Several large population-based studies have suggested that patients with herpes zoster have an increased risk of occult cancer.[3–7] These findings have instigated discussion of whether patients with herpes zoster should be examined for cancer in order to expedite diagnosis and ultimately improve prognosis.[3,4,7–9] Although such discussions should rely on a sound evidence base, no systematic review exists of studies on the topic. In particular, the types of cancers that are most likely to be associated with reactivation of latent varicella-zoster virus are yet to be uncovered systematically.

The aim of this systematic review was to collate evidence on the association between herpes zoster and the risk of subsequent cancer diagnosis. Because the primary interest was occult cancer, the main focus was on cancer diagnosed in the first year following herpes zoster compared with persons without herpes zoster. As a secondary aim, we specifically examined which cancer types are most strongly associated with herpes zoster.

Materials and methods

Search strategy and eligibility criteria

We conducted the study according to The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines[11] (Web Methods 1 and 2). We formulated the study protocol (available from study authors upon request) in accordance with PRISMA for protocols,[12,13] with slight modifications to increase applicability to the non-interventional subject under consideration.

In collaboration with a trained librarian, we performed a comprehensive literature search of the MEDLINE (PubMed) and EMBASE electronic databases to identify studies published on the association between herpes zoster and cancer before February 1, 2015 (Web Methods 3 outlines the search strings). We also searched reference lists of eligible articles to identify further potentially relevant studies. On February 18, 2016, we updated the search.

Studies were eligible for inclusion if (1) herpes zoster was included as an exposure or predictor, (2) the outcome was overall cancer or one or more specific subtypes of cancer, and (3) a control group was included, i.e., controls without cancer in case-control studies or a comparison cohort without herpes zoster or a similar reference population (e.g., a general population sample) in cohort studies. We did not consider myelodysplastic and myeloproliferative syndromes not classified as neoplasms in the 10th revision of the International Classification of Diseases by the World Health Organization. We imposed no restrictions to publication year, study population or setting (inpatients, outpatients, or general practice), design, eligibility criteria, length of follow-up, or statistical analyses applied. Besides English language papers, we aimed to include publications in other languages known by the authors or by consulting colleagues. Meeting abstracts or studies published as abstract only were not eligible.

Study selection and data extraction

One investigator (SAJS) performed the initial screening of titles and abstracts and retrieved full-text reports of potentially eligible studies. Subsequently, two investigators (SAJS, AM) performed independent eligibility assessment of the retrieved reports using the eligibility criteria listed above. The two authors also performed data extraction by using a piloted data abstraction sheet including the following data: author, journal, publication year, study design, setting, study period, eligibility criteria, study size, age and sex distribution, data source for herpes zoster, data source for cancer diagnosis, comparator group (description of standard population or comparison cohort in cohort studies or controls in case-control studies), length of follow-up, type of relative risk estimate, statistical method used (e.g., logistic regression), maximum variables controlled for, and the maximally adjusted estimate for cancer overall, cancer subtype, and time points considered. When effect estimates were unobtainable, we extracted the raw data. As a measure of precision, we obtained 95% confidence intervals (CIs). When the 95% CI for an estimate was not reported, we retrieved the standard error, the exact p-value, estimation from a figure/graph, or raw data, listed in order of priority. Any disagreements between reviewers were resolved by consensus. When data was unreported or unclear, we sought to contact the corresponding author for clarification. Where multiple overlapping publications were included after the initial eligibility assessment, we agreed to use the most recent and inclusive report.

Risk of bias assessment

There is no consensus regarding the use of scoring tools for assessing risk of bias in non-randomized studies.[11] We therefore identified key design elements that could potentially bias study estimates, including sources of potential selection bias (non-participation in case-control studies, use of hospital controls in case-control studies, and loss to follow-up in cohort studies), information bias (self- or proxy-report of herpes zoster, and potential misclassification of herpes zoster or cancer), and lack of control for age and/or sex. The two reviewers performed the risk of bias assessment independently.

Statistical analyses

We illustrated the results for individual studies graphically using forest plots for each outcome. We considered measures of relative risk (odds ratios, risk ratios, rate ratios, hazard ratios) to be equivalent. Although this assumption is suboptimal compared with pooling individual-level data (not available), we considered the measures equivalent

because included studies considered the same exposure and outcome and the outcome was relatively rare.[14,15] When adjusted effect estimates were unobtainable, we used the raw data to calculate relative risk estimate and 95% CIs. When only the point estimate and the p-value was available, we used the method described by Altman et al. to compute the CI.[16]

We pooled estimates for any cancer overall and for cancers diagnosed within one year after herpes zoster using a random-effects model.[17] For studies with information on cancer subtypes, we also pooled the estimates for individual cancer types. We assessed statistical heterogeneity using the I^2 statistic.[18]

To examine the robustness of our results and to explore sources of heterogeneity, we performed several pre-planned subgroup and sensitivity analyses. To examine if temporal advances in diagnostic techniques may have modified the association, we performed analyses according to calendar year of publication. We repeated analyses after excluding studies with a high risk of bias, including studies where a history of cancer before herpes zoster was not specified as an exclusion criterion, where the comparator group may not be representable of the source population (e.g., hospital/disease controls), where information on herpes zoster was based on self- or proxy-report, or where age and/or sex was not accounted for in analyses, case-control studies with non-participation. Several studies excluded the first two months in the analyses, because of concerns about inaccurate data on sequence of events, i.e., to be certain the cancer diagnosis and treatment had not been initiated before herpes zoster diagnosis. To examine if this difference in follow-up start affected the results, we also performed a *post hoc* meta-analysis for the association between herpes zoster and cancer diagnosed between two months and one year of follow-up.

Our main focus was on relative risk measures, as they could be obtained regardless of design. Additionally, we retrieved absolute risk of cancer within the first year of follow-up from the studies on overall cancer. Assuming that diagnostic work-up would have facilitated diagnosis of these occult cancers at the time of presentation with herpes zoster, we estimated the number of patients needed

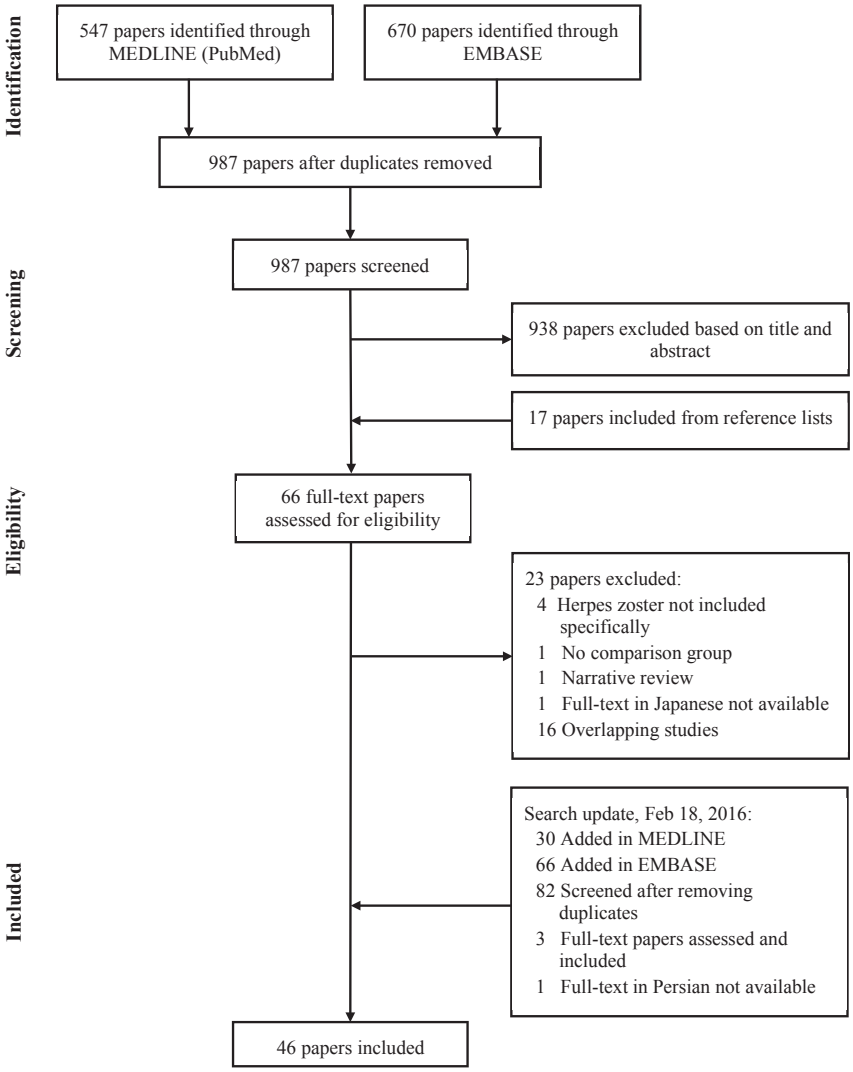

Figure 1 Flowchart describing study selection.

Table 1 Characteristics of studies on herpes zoster and risk of any subsequent cancer.

Lead author, year (reference no.)	Study region and period	Design	Participants	Method of identifying zoster (lag period)[a]	Method of identifying cancer	Age (y)[b]	Male (%)[b]	Analysis (adjustment)
Buntinx, 2014[7]	Flanders, Belgium, 1994–2008	Cohort	4821 zoster patients and comparison cohort of 23,421 persons matched by birth year, sex and date	Intego GP-based registry (no lag)	Intego GP-based registry	47	45%	Cox (age, sex)
Chiu, 2013[5]	Taiwan, 1997–2006	Cohort	38,743 ambulatory zoster patients and comparison cohort of 116,229 persons individually matched by age, sex and date	TNHIRD (2 mos.)	TNHIRD	N.R.	53%	Cox (age, sex, urbanization level of residence, insurance level, DM, CCI for past 12 months)
Cotton, 2013[3]	UK, 2001–2002	Cohort	13,428 zoster patients and a comparison cohort of 60,601 patients matched by sex and birth year	GPRD (no lag)	GPRD	60	42%	Cox (age, sex)
Fueyo, 1984[43]	Pennsylvania, US, 1977–1980	Cohort	50 outpatients with zoster[c] diagnosed in two family practices	M.R. (no lag)	M.R. and telephone interview	N.R.	32%	Indirect standardization (age)
Guess, 1985[44]	Rochester, Minnesota, US, 1960–1981	Cohort	173 children and adolescents with zoster	M.R. (no lag)	M.R.	N.R.	51%	Indirect standardization (age)
Iglar, 2013[6]	Ontario, Canada, 1993–2010	Cohort	542,575 zoster patients and a comparison cohort with 542,575 persons matched by age, sex and date	Physician billing database in the Ontario Health Insurance Plan (no lag)	Ontario Cancer Registry	54	41%	Cox (urban/rural setting, area-level income, MI, asthma, COPD, congestive heart failure, DM, hypertension)
Mahale, 2016[45]	Multiple US sites, 1992–2005	CC	1,108,986 cases with cancer and 100,000 frequency-matched controls	SEER-Medicare database: Inpatient or $\geq$2 physician or outpatient claims for zoster $\geq$30 days apart (1 y)	SEER-Medicare database	N.R.	53%	LR (age, sex, year of selection, race, average annual number of physician claims $>$1 year case/control identification)
Ragozzino, 1982[46]	Rochester, Minnesota, US, 1945–1959	Cohort	590 zoster patients	M.R. (no lag)	M.R. for observed cancers, regional cancer incidence for reference	N.R.	41%	Indirect standardization (age, sex)

Sørensen, 2004[4]	Denmark, 1977–1996	Cohort	13,414 inpatients with zoster	Danish National Patient Registry (2 mos.)	Danish Cancer Registry	72	38%	Indirect standardization (age, sex, year, cancer site)
Yamamoto, 2003[8]	Single hospital, Japan, 1990–1999	Cohort and CS	131 zoster patients in CS substudy, 140 in the cohort substudy	Hospitalization with zoster (no lag)	Work-up for cancer during hospitalization[d]; Mailed questionnaires for FU for cancer	67	41%	Indirect standardization (N.R.)

Abbreviations: CCI = Charlson comorbidity index; COPD = Chronic obstructive pulmonary disease; Cox = Cox proportional hazards regression; CS = Cross-sectional; DM = Diabetes mellitus; FU = follow-up; GP = General practitioner; GPRD = General Practice Research Database; LR = Logistic regression; MI = Myocardial infarction; M.R. = Medical record review; N.R. = Not reported; PY = Person-years; TNHIRD = Taiwan National Health Insurance Research Database.

[a] The lag period is the time period during which any association between herpes zoster and cancer was ignored.

[b] When the percentage of males or the mean/median age was reported separately for cases and controls or herpes zoster patients and the comparison cohort in a study, we used their average.

[c] Included also a comparison cohort of psoriasis patients. Because these patients may have an increased risk of cancer, we focused on the results from the indirect standardization to general population.

[d] Work-up included X-ray of chest and abdomen, GI endoscopy, total colonoscopy/barium enema, and abdominal CT scan.

to examine at time of diagnosis to detect one cancer. This was computed as the inverse of the excess risk of cancer among herpes zoster patients, thus corresponding to the 'number needed to treat'.[19]

We evaluated the possibility for small study effects, including publication bias, by visual inspection of funnel plots constructed by plotting the effect estimate in each study by the inverse of its standard error. All analyses were performed using STATA software, version 12.1 (StataCorp LP, College Station, TX).

Results

Systematic literature search

The search identified 987 unique papers in PubMed and EMBASE (Fig. 1). We excluded 938 papers after scrutinizing titles and abstract, leaving 49 papers for full-text assessment. We additionally identified 17 papers from reference lists and 4 papers when updating the search. We excluded six ineligible studies,[20–25] two non-English studies that could not be retrieved in full-text,[9,26] and 16 studies with duplicate data.[27–42] Finally, the review thus encompassed 46 papers reporting results for any type of cancer.[3–8,43–82] For thirteen studies that demonstrated overlapping data for some cancer subtypes, we selected the study presenting the most detailed data for that particular cancer. Characteristics of studies that were partly or entirely excluded after the initial screening are shown in Web Table 1. Disagreements between reviewers during the study selection were resolved by consensus as outlined in Web Table 2.

Overall cancer

Study characteristics and risk of bias

Ten studies reported on the association between herpes zoster and overall cancer (Table 1); one case-control study[45] and nine cohort studies.[3–8,43,44,46] The number of herpes zoster patients followed in the cohort studies was 613,925, ranging from 50 to 542,575. The case-control study included approximately 1.8 million cancer cases and 100,000 controls.

The first three studies on herpes zoster and subsequent cancer were published in the 1980s.[43,44,46] Besides a small sample size, we identified several shortcomings. First, herpes zoster patients with previous cancer were not excluded. Among patients with a history of cancer, herpes zoster is probably more likely to be caused by cancer therapy (e.g., chemotherapy) than by another undiagnosed cancer, thus leading to potential underestimation of the association. On the other hand, individuals with a history of cancer, have an increased risk of both herpes zoster[2,83] and of new primary cancer,[84] which would bias estimates in the opposite direction, in particular for long-term survivors. Second, the study by Guess et al. was restricted to children and adolescents, in whom the prevalence of risk factors for herpes zoster and the types of cancer most frequently observed differ from adults.[85] Third, standardization methods were potentially inaccurate. Two studies did not standardize by sex[43,44] and one study used broad age bands.[43]

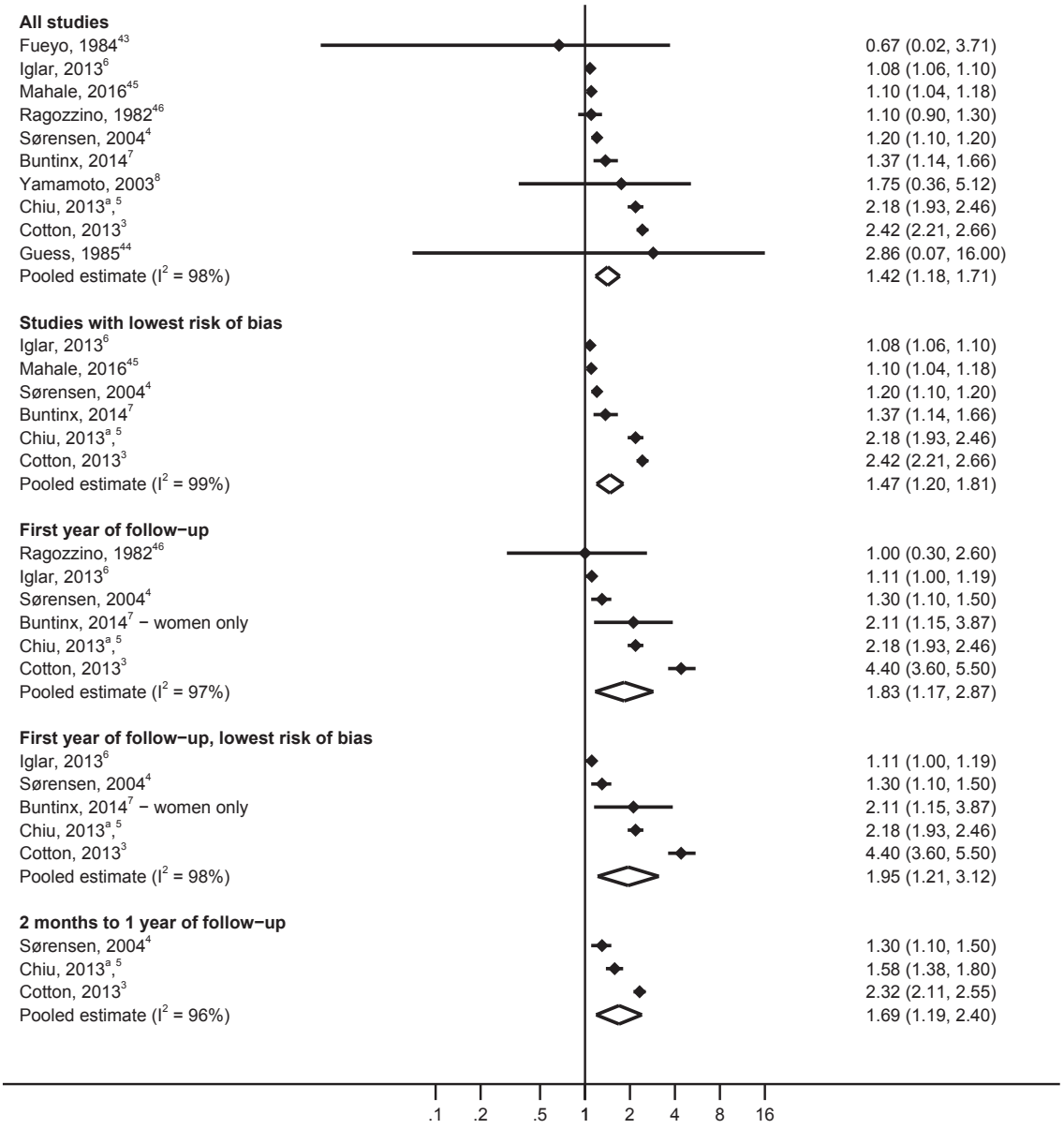

Figure 2 Relative risk estimates (95% confidence intervals) for the association between herpes zoster and subsequent diagnosis of overall cancer, ordered according to the magnitude of the effect estimate. [a]The estimate from the study by Chiu et al. represents the relative risk at 1 year, as an overall estimate was not reported.

Ragozzino et al. followed patients up for histologically verified cancer, while the expected numbers were based on total number of cancers in the general population, which likely includes both histologically and non-histologically verified cancers.[46] Thus, the resulting standardized incidence ratios of cancer may underestimate the true relative risk. Finally, the study by Fueyo et al. required at least two years of follow-up for all participants, thereby potentially excluding patients with fatal cancer during this period, which may have occurred more frequently in the herpes zoster group.[43] Two studies reported data on subsequent cancer among hospitalized patients with herpes zoster.[4,8] In a study by Yamamoto et al.,[8] herpes zoster patients were invited to participate in work-up for cancer during admission and subsequent follow-up for cancer through questionnaires mailed after discharge. It is possible that the risk of cancer during follow-up was underestimated due to a compensatory deficit in herpes zoster patients who also participated in the work-up during admission. The use of questionnaires for follow-up may also have introduced bias, because it conditions on survival at the time of follow-up and because cancer patients may be more or less inclined to reply depending on their physical or psychological state. The second hospital-based study by Sørensen et al.[4] was based on nationwide registry data and considered to be at lower risk of bias. Assuming that the registry diagnoses for herpes zoster were accurate, the lack of data on herpes zoster diagnosed outside the hospital would have little influence on the internal validity, resulting in a slight

bias towards the null at most.[86] Nevertheless, hospitalized patients possibly represent a selected group of patient, potentially limiting generalizability to milder cases if the association depends on severity of infection.

The five remaining studies were large studies including patients diagnosed with herpes zoster in primary care (outpatients) and the hospital-based setting.[3,5–7,45] Except for a potential incomplete follow-up in the registries used (e.g., due to patients seeking treatment outside the study setting),[3,7,45] we judged internal validity to be high.

Meta-analyses

We observed large statistical heterogeneity, as indicated by an overall I^2 statistic of 98%. Nevertheless, because studies consistently pointed in the same direction (increased cancer risk in herpes zoster patients), we decided to pool the results using a random-effects model and also explore sources of heterogeneity.

The pooled relative risk for the association between herpes zoster and any cancer was 1.42 (95% CI: 1.18, 1.71) when considering all ten studies and 1.47 (95% CI: 1.29, 1.81) when restricting to studies with the lowest risk of bias (Fig. 2). Statistical heterogeneity, however, remained high. The results did not vary systematically by publication year (Web Fig. 1).

We included six studies in the meta-analysis of cancer within the first year following herpes zoster, yielding a pooled relative risk of 1.83 (95% CI: 1.17, 2.87). This estimate was 1.95 (95% CI: 1.21, 3.12) when restricting to studies with lowest risk of bias. When combining studies where the first two months of follow-up had been excluded, the relative risk was 1.69 (95% CI: 1.19, 2.40). We did not combine results beyond the first year of follow-up, because the time periods used varied largely. Nevertheless, detailed inspection of the results according to time between herpes zoster and cancer in each study (Web Table 3) shows that in general the relative risk estimates decreased with increasing time between diagnoses.

Two studies included data on stage of cancer at the time of diagnosis. In the study by Sørensen et al.,[4] the prevalence ratio of distant metastasis was 1.07 (95% CI: 0.92, 1.23) for cancer patients with previous herpes zoster compared with those without such history. Mahale et al.[45] similarly reported that the odds ratio for the association between herpes zoster and cancer was highest for regional- or distant-stage cancer. However, stage-specific results were only provided for selected cancers, which were chosen based on statistical significance in the main analyses.

The absolute risk of cancer within the first year after herpes zoster varied from 0%[43,44] to 1.8% among inpatients[4] (Table 2). In the study by Yamamoto et al., extensive examination revealed occult cancer among 4.6% of patients admitted with herpes zoster. Four studies provided data enabling an estimation of the number of patients needed to examine to detect one excess cancer at the time of presentation with herpes zoster; the number varied from 114[3] to as much as 771.[6]

Hematological cancers

Study characteristics and risk of bias

We included 37 studies reporting data on the association between herpes zoster and one or more types of hematological cancer. Characteristics for the studies are shown in Table 3, except for five cohort studies[3,4,6,7,46] already described in Table 1.

Methodological limitations were common (Web Table 4). A case-control design was used in 27 studies, which generally had the highest risk of bias. For example, 18 studies assessed history of herpes zoster through self- or proxy-report,[47,50–52,54–56,58–61,68,69,71,75–77] without medical record verification in most studies. Eight case-control studies

Table 2 Absolute effect measures reported in cohort studies on any cancer diagnosis in the first year following herpes zoster.

Lead author, year (reference no.)	Absolute risk		Risk difference (95% confidence interval)	Number needed to examine to detect one excess cancer (95% confidence interval)
	Herpes zoster cohort	Comparison cohort		
Buntinx, 2014[a,7]	~1.0% (26/2635)	~0.5% (64/12827)	~0.49% (0.09%, 0.88%)	~204 (114, 1111)
Chiu, 2013[5]	0.97% (376/38743)	0.59% (689/116229)	0.38% (0.27%, 0.48%)	265 (208, 370)
Cotton, 2013[3]	1.1% (154/13428)	0.27% (162/60601)	0.88% (0.69%, 1.06%)	114 (94, 145)
Fueyo, 1984[43]	0% (0/50)	N.R.[b]	N.R.	N.R.
Guess, 1985[44]	0% (0/173)	N.R.[b]	N.R.	N.R.
Iglar, 2013[6]	1.0% (5615/542575)	0.91% (4911/542575)	0.13% (0.09%, 0.17%)	771 (588, 1111)
Ragozzino, 1982[46]	0.68% (4/590)	N.R.[b]	N.R.	N.R.
Sørensen, 2004[4]	1.8% (188/10588)	N.R.[b]	N.R.	N.R.
Yamamoto, 2003[8]	4.6% (6/131)[c]	N.R.[b]	N.R.	N.R.

Abbreviations: N.R. = Not reported.

[a] Provided absolute risk data only for women in a Kaplan–Meier figure. The data provided are thus based on eye-balling the figure to get the percentage of cancers diagnosed in herpes zoster patients and comparators and subsequent back-calculation to get the absolute numbers.

[b] Standardized the results to the general population and provided only the expected number of cancer. As the person-years of follow-up for the first year were not provided, the risk difference and number needed to examine could not be estimated.

[c] Detected by offering admitted herpes zoster patients work-up with X-ray of chest and abdomen, GI endoscopy, total colonoscopy/barium enema, and abdominal CT scan.

Table 3 Characteristics of studies on herpes zoster and risk of subsequent hematological cancer.[a]

Lead author, year (reference no.)	Study region and period	Design	Participants	Method of identifying zoster (lag period)[b]	Method of identifying cancer	Age (y)[c]	Male (%)[c]	Analysis (adjustment)
Amadori, 1995[47]	Forlí province, Italy, 1987–1990	CC	187 NHL and CLL cases and 977 controls frequency-matched by age and sex through residents' list	Self- or proxy-reported (2 y)	Romagna Cancer Registry	63[d]	56%	LR (age, sex, altitude of municipality, 1. degree familial hematological cancer)
Anderson, 2014[48]	Multiple US sites, 1992–2005	CC	44,191 NHL cases, 1832 HL cases, and 200,000 controls frequency-matched by age, sex, and year among Medicare beneficiaries in SEER areas	SEER-Medicare database (13 mos.)	SEER-Medicare database	N.R.	49%	LR (age, sex, year of diagnosis/ selection)
Anderson, 2009[49]	Multiple US sites, 1993–2002	CC	10,171 CLL cases and 122,531 controls frequency-matched by age, sex, and y among Medicare beneficiaries in SEER areas	SEER-Medicare database (1 y)	SEER-Medicare database	77	52%	LR (age, sex, race, calendar year of diagnosis/ selection, number of physician claims)
Andreotti, 2015[50]	Multiple US sites, 2003–N.R.	CC	481 patients MM and 351 spouse controls	Self-reported after age 20 y (1 y)	Included through relevant clinical institutions and awareness campaigns in the MM community	64	48%	LR (age, sex, race, education, and BMI)
Becker, 2012[51]	Multicenter (US, UK, Italy, Australia), 1983–2005	CC	6061 NHL cases and 8531 controls (hospital-/ population-based and frequency/individual matched or not depending on site)	Self-reported (2 y)	Various	59[d]	54%[d]	Random effects LR (age, sex, study center)
Bernstein, 1992[52]	Los Angeles County, US, 1979–1982	CC	619 NHL cases and 619 neighborhood controls individually matched by birth year, race and sex	Self-reported (no lag)	Cancer Surveillance Program, Los Angeles County	57	46%	Crude

Brown, 2008[53]	VA hospitals, US, 1969—1996	Cohort	4,501,578, among whom 4641 got MM	Discharge record at VA hospital (1 y)	Discharge record at VA hospital	55	100%	Poisson (age, calendar y, race, no. of hospital visits, latency between study entry and exit)
Cartwright, 1988[54]	Yorkshire region, England, 1979—1984	CC	437 NHL cases and 724 individually matched hospital controls matched by residential health district, sex, and age	Self-reported, verified by M.R. (no lag)	Regional cancer registry, histopathology laboratories and lymphoma panel	N.R.	56%	MH (age, sex)
Cartwright, 1987[55]	Yorkshire region, England, 1979—1984	CC	245 CLL, 85 MLL cases, and 561 individually matched hospital controls matched by residential health district, sex and age	Self-reported, verified by M.R. (no lag)	Regional cancer registry, histopathology laboratories and lymphoma panel	N.R.	N.R.	MH (age, sex)
Cuzick, 1988[56]	Six regions, England and Wales, 1978—1984	CC	399 MM cases and 399 hospital controls individually matched by age and sex	Self-reported, verified by M.R. (1 y)	Referral center patient files	N.R.	52%	Crude
Doody, 1992[57]	Portland, 1959—79 and Northern California, 1956—1982	CC	299 leukemia cases, 100 NHL cases, and 175 MM cases and 787 controls individually matched by sex, age, number of years in program, and calendar year for membership start	M.R. (5 y)	Kaiser Permanente Medical Care Program	62	60%	Crude
Gibson, 1976[58]	Various counties in New York, Maryland, and Minnesota, US, 1959—1962	CC	605 leukemia cases and 668 population controls from same geographic area	Self- or proxy-reported physician-diagnosed (1 y)	Cancer Registry of the New York State Department of Health and study case-reporting system	N.R.	100%	Cochran's weighted chi-square (age)

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Table 3 (*continued*)

Lead author, year (reference no.)	Study region and period	Design	Participants	Method of identifying zoster (lag period)[b]	Method of identifying cancer	Age (y)[c]	Male (%)[c]	Analysis (adjustment)
Gramenzi, 1991[59]	Greater Milan area, Italy, 1983–1989	CC	117 MM cases and 477 hospital controls	Self-reported (1 y)	Admission to cancer institutes and various hospitals/clinics in study area	61	61%	LR (age, sex, residential area, education, various other infectious and inflammatory diseases, immunizations; age and sex in analyses according to time)
Karunanayake, 2012[60]	Six provinces, Canada, 1991–1994	CC	316 HL cases, 513 NHL cases,[d] and 1506 controls frequency-matched by age and province from provincial health insurance, phone or voter's lists	Self-reported (no lag)	Provincial Cancer Registries, except for a hospital ascertainment in Quebec	51	100%	LR (age, province,[d] HL also for use of four pesticides, diagnosis with infectious mononucleosis for HL)
Koepsell, 1987[61]	Various counties in Utah, Washington, Georgia, Michigan, US, 1977–1981	CC	689 MM cases and 1681 frequency-matched residential controls through RDD or selection of households	Self- or proxy-reported (no lag)	Cancer registries	N.R.	54%	MH (age, sex, race, study area, education)
Koshiol, 2011[62]	VA hospitals, US, 1969–1996	Cohort	4,501,578, among whom 9496 developed NHL	Discharge record at VA hospital (1 y)	Discharge record at a VA hospital	52	100%	Poisson (age, calendar year, race, no. of hospital visits, latency between study entry and exit)
Koshiol, 2008[63]	VA hospitals, US, 1969–1996	Cohort	4,501,278 among whom 361 developed WM	Discharge record at VA hospital (1 y)	Discharge record at a VA hospital	53	100%	Poisson (age, calendar year, race, no. of hospital visits, latency between study entry and exit)

Kristinsson, 2015[64]	Sweden, 1965—2004	CC	7414 HL cases and 29,240 population controls matched by sex, birth year, and county of residence	Admission with zoster in the Swedish Patient Registry (1 y)	The Swedish Cancer Registry	47	59%	LR (birth year, sex, calendar y of index date, county)
Kristinsson, 2011[65]	Sweden, 1965—2004	CC	9219 AML cases and 36,389 population controls matched by sex, birth year, and county of residence	Admission with zoster in the Swedish Inpatient Registry (1 y)	The Swedish Cancer Registry	68	53%	LR (birth year, sex, calendar y of index date, county)
Kristinsson, 2010[66]	Sweden, 1958—2005	CC	2470 LPL/WM cases and 9698 population controls matched by sex, birth year, and county of residence	Admission with zoster in the Swedish Inpatient Registry (1 y)	The Swedish Cancer Registry, Inpatient Registry and authors' network of hematology/oncology centers	74	59%	LR (birth year, sex, calendar y of index date, county)
Landgren, 2007[67]	VA hospitals, US, 1969—1996	Cohort	4,501,578 among whom 3680 developed CLL	Discharge record at VA hospital (1 y)	Discharge record at a VA hospital	53	100%	Poisson (age, calendar y, race, no. of hospital visits, latency between study entry and exit)
La Vecchia, 1992[68]	Greater Milan area, Italy, 1983—1990	CC	177 NHL cases and 561 hospital controls	Self-reported (1 y)	Admission to cancer institutes and various hospitals/clinics in study area	59	67%	MH and LR (age, sex, scarlet fever, pyelonephritis, tonsillectomy, chronic inflammatory disease, residential area, education. Only age and sex in analyses according to time)
Lewis, 1994[69]	Georgia, Michigan, New Jersey, US, 1986—1989	CC	573 MM cases and 2131 frequency-matched population-based controls through RDD and Medicare files	Self-reported physician-diagnosed (1 y)	Hospital pathology, hematology, outpatient, and tumor registry records, and rapid case-reporting system	63	56%	LR (age, sex, education, study site, race)

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Table 3 (*continued*)

Lead author, year (reference no.)	Study region and period	Design	Participants	Method of identifying zoster (lag period)[b]	Method of identifying cancer	Age (y)[c]	Male (%)[c]	Analysis (adjustment)
Liu, 2012[70]	Taiwan, 1996—2007	Cohort	42,498 zoster patients and comparison cohort of 169,983 persons individually matched by age, sex, and date	TNHIRD (6 mos.)	TNHIRD	49	48%	Cox (age, sex, CCI comorbidities, income)
McKinney, 1990[71],[e]	Yorkshire region, England, 1979—1986	CC	248 HL cases, 122 CML cases, 64 ALL cases, 161 AML cases and 1159 individually matched hospital controls matched by residential health district, sex, and age	Self-reported, verified by M.R. (1 y)	Regional cancer registry, histopathology laboratories and lymphoma panel	N.R.	59%	LR (age, sex, area of residence)
McShane, 2014[72]	Multiple US sites, 1992—2005	CC	693 LPL/WM cases and 200,000 controls frequency-matched by age, sex, and year among Medicare beneficiaries in SEER areas	SEER-Medicare database (13 mos.)	SEER-Medicare database	N.R.	50%	LR (age, sex, calendar period)
McShane, 2014[73]	Multiple US sites, 1992—2005	CC	15,318 MM cases and 200,000 controls frequency-matched by age, sex, and year among Medicare beneficiaries in SEER areas	SEER-Medicare database (13 mos.)	SEER-Medicare database	N.R.	51%	LR (age, sex, calendar period)
Nanni, 1998[74]	Forlí province, Italy, 1987—1990	CC	46 MM cases and 230 controls frequency-matched by age and sex from residents' list	Self- or proxy-reported (N.R., possibly 2 y)	Romagna Cancer Registry	64	57%	LR (age, sex, educational level, familiarity for hematological tumors, altitude of residence)

Pahwa, 2012[75]	Six provinces, Canada, 1991–1994	CC	342 MM cases and 1506 controls frequency-matched by age and province from provincial health insurance, phone or voter's lists	Self-reported (no lag)	Provincial Cancer Registries, except for hospital ascertainment in Quebec province	59	100%	LR (age, province, measles, allergies, arthritis, family history of cancer, exposure to non-pesticide chemicals, carbaryl, captan)
Parodi, 2012[76]	Savona Province, Italy, 2002–2005	CC	125 lymphoid and 40 myeloid cases of hematological cancer and 233 controls frequency-matched by sex and age from population health registry	Self-reported (no lag)	M.R.	64	57%	LR (age, sex)
Tavani, 2000[77]	Pordenone, Italy, 1983–1992	CC	158 HL cases and 1157 hospital controls	Self-reported (1 y)	Admission to cancer institutes and general hospitals in study area	49	59%	LR (age, sex, education)
Titmarsh, 2014[78]	Multiple US sites, 1992–2005	CC	8489 AML cases, 3626 CML cases, and 200,000 controls frequency-matched by age, sex, and year among Medicare beneficiaries in SEER areas	SEER-Medicare (1 y) database	SEER-Medicare database	63	53%	LR (age, sex, calendar period)

Abbreviations: ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CC = case-control; CCI = Charlson comorbidity index; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; COPD = chronic obstructive pulmonary disease; Cox = Cox proportional hazards regression; CS = Cross-sectional; DM = Diabetes mellitus; DNPR = Danish National Patient Registry; FU = follow-up; GP = General practitioner; GPRD = General Practice Research Database; HL = Hodgkin's lymphoma; LPL = lymphoplasmacytic lymphoma; LR = Logistic regression; MH = Mantel-Haenzel; MLL = malignancy lymphoma-lymphocytic form; MI = Myocardial infarction; MM = multiple myeloma; M.R. = Medical record review; NHL = Non-Hodgkin's lymphoma; N.R. = Not reported; Poisson = Poisson regression; PY = Person-years; RDD = random digit dialling; TNHIRD = Taiwan National Health Insurance Research Database; VA = Veterans Affairs; WM = Waldenström's macroglobulinemia.

[a] Five studies by Cotton et al., Sørensen et al., Buntinx et al., Iglar et al., and Ragozzino et al. reported data on overall cancer as well as hematological cancer. Characteristics for these studies are shown in Table 1.

[b] The lag period is the time period during which any association between herpes zoster and cancer was ignored.

[c] When the percentage of males or the mean/median age was reported separately for cases and controls or herpes zoster patients and the comparison cohort in a study, we used their average.

[d] For 17 studies included in the multicenter study, among which only 8 were included in the analysis of herpes zoster.

[e] Information provided/confirmed by author. Study also included 357 soft tissue sarcoma cases, as presented in Table 4.

Table 4 Characteristics of studies on herpes zoster and risk of non-hematological cancer.[a]

Lead author, year (reference no.)	Study region and period	Design	Participants	Method of identifying zoster (lag period)[b]	Method of identifying cancer	Age (y)[c]	Male (%)[c]	Analysis (adjustment)
Franceschi, 1992[79]	Pordenone, Italy, 1985—1991	CC	93 STS cases and 721 hospital controls	Self-reported (1 y)	In- or outpatient treatment at Aviano Cancer Central or general hospitals in study area	53 y	54%	MH (age, sex)
Karunanayake, 2012[60,d]	Six provinces, Canada, 1991—1994	CC	357 STS cases and 1506 controls frequency-matched by age and province from provincial health insurance, phone or voter's lists	Self-reported (no lag)	Provincial Cancer Registries, except for a hospital ascertainment in Quebec	55 y	100%	LR (age, province)
Scheurer, 2008[80]	Houston, Texas, US, 2001—2006	CC	325 glioma cases and 600 controls frequency-matched by age, sex, and ethnicity through RDD	Self- or proxy-reported (no lag)	M.R., confirmed by neuropathologist	50 y	55%	Crude
Wrensch, 1997[81]	San Francisco Bay Area, US, 1991—1994	CC	450 glioma cases and 440 controls frequency-matched by age, sex, and ethnicity through RDD	Self- or proxy-reported (no lag)	The Northern California Cancer Centre's rapid case ascertainment system	54 y	56%	LR (age, sex)
Wrensch, 2005[82]	San Francisco Bay Area, US, 1997—1999	CC	401 glioma cases and 402 controls frequency-matched by age, sex, and ethnicity through RDD	Self- or proxy-reported (no lag)	Northern California Cancer Centre's rapid case ascertainment system	56 y	55%	LR (age, sex, ethnicity)

Abbreviations: CC = case-control; LR = Logistic regression; MH = Mantel-Haenzel; M.R. = Medical record review; RDD = random digit dialling.

[a] Seven studies by Buntinx et al., Chiu et al., Cotton et al., Iglar et al., Mahale et al., Ragozzino et al. and Sørensen et al. reported data on overall cancer as well as hematological cancer. Characteristics for these studies are shown in Table 1.

[b] The lag period is the time period during which any association between herpes zoster and cancer was ignored.

[c] When the percentage of males or the mean/median age was reported separately for cases and controls or herpes zoster patients and the comparison cohort in a study, we used their average.

[d] Information provided/confirmed by author. The study also included Hodgkin and Non-Hodgkin's lymphoma, as presented in Table 3.

used hospital controls,[50,51,54–56,59,68,71,77] which may have resulted in a non-representative sample of the frequency of herpes zoster in the source population. For example, some studies excluded controls with immunological or chronic conditions,[51,56,68,77] which may be associated with herpes zoster.[87] Selection bias due to differential participation is another potential limitation in 19 case-control studies where up to 55% of cases were excluded for various reasons, including that patients had died or were too ill to cooperate.[47,50–52,54–61,68,69,71,74–77] If herpes zoster is a marker of particularly aggressive cancers, exclusion of these patients may have resulted in underestimation of the association. Finally, three matched case-control studies presented crude data only.[52,56,57]

The cohort studies used secondary data from electronic registries or medical records. Although some degree of non-differential misclassification is expected in most studies, the risk of bias was generally lower in the cohort studies. We also judged eight of the case-control studies to have a lower risk of bias,[48,49,64–66,72,73,78] because they did not use

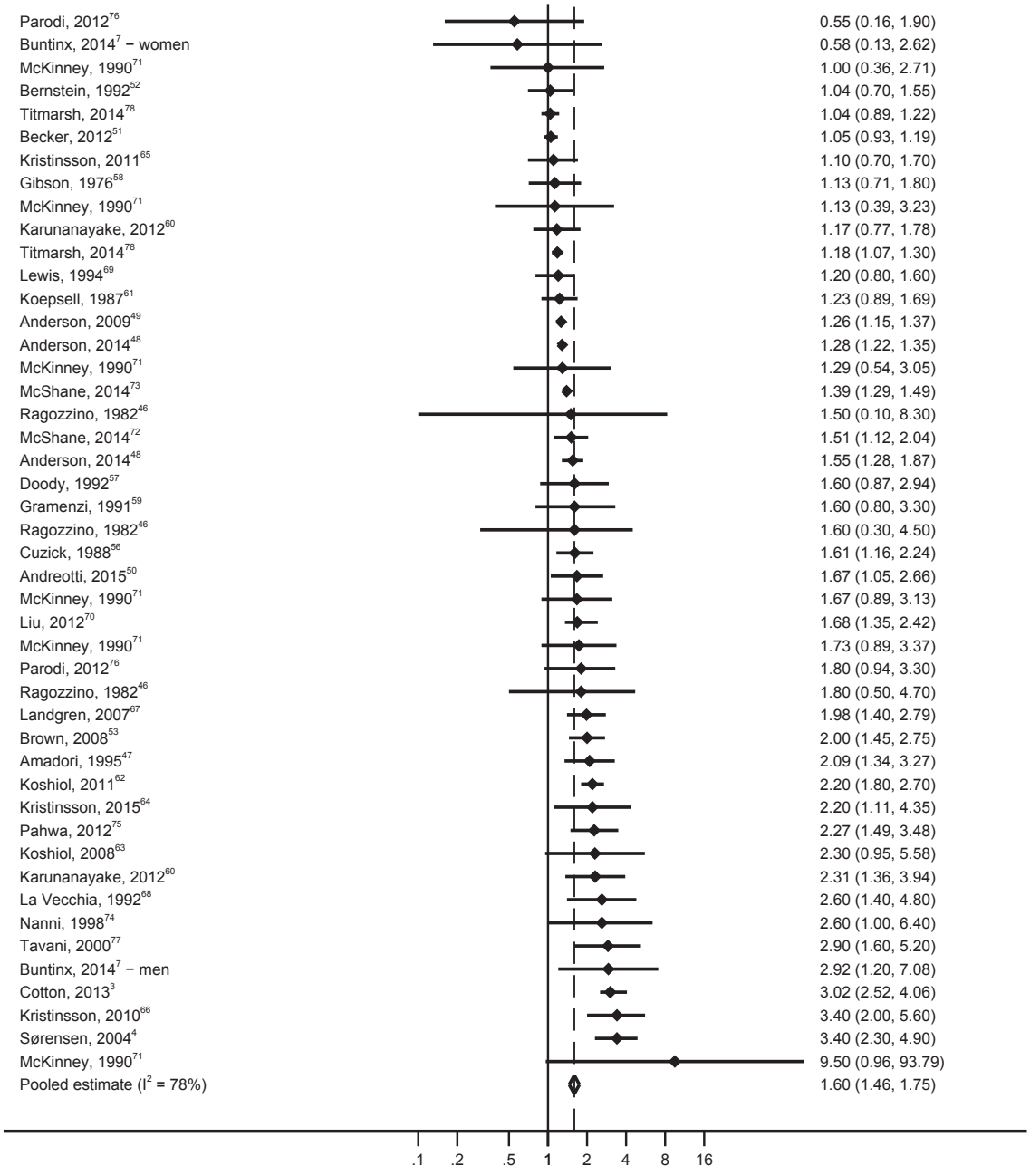
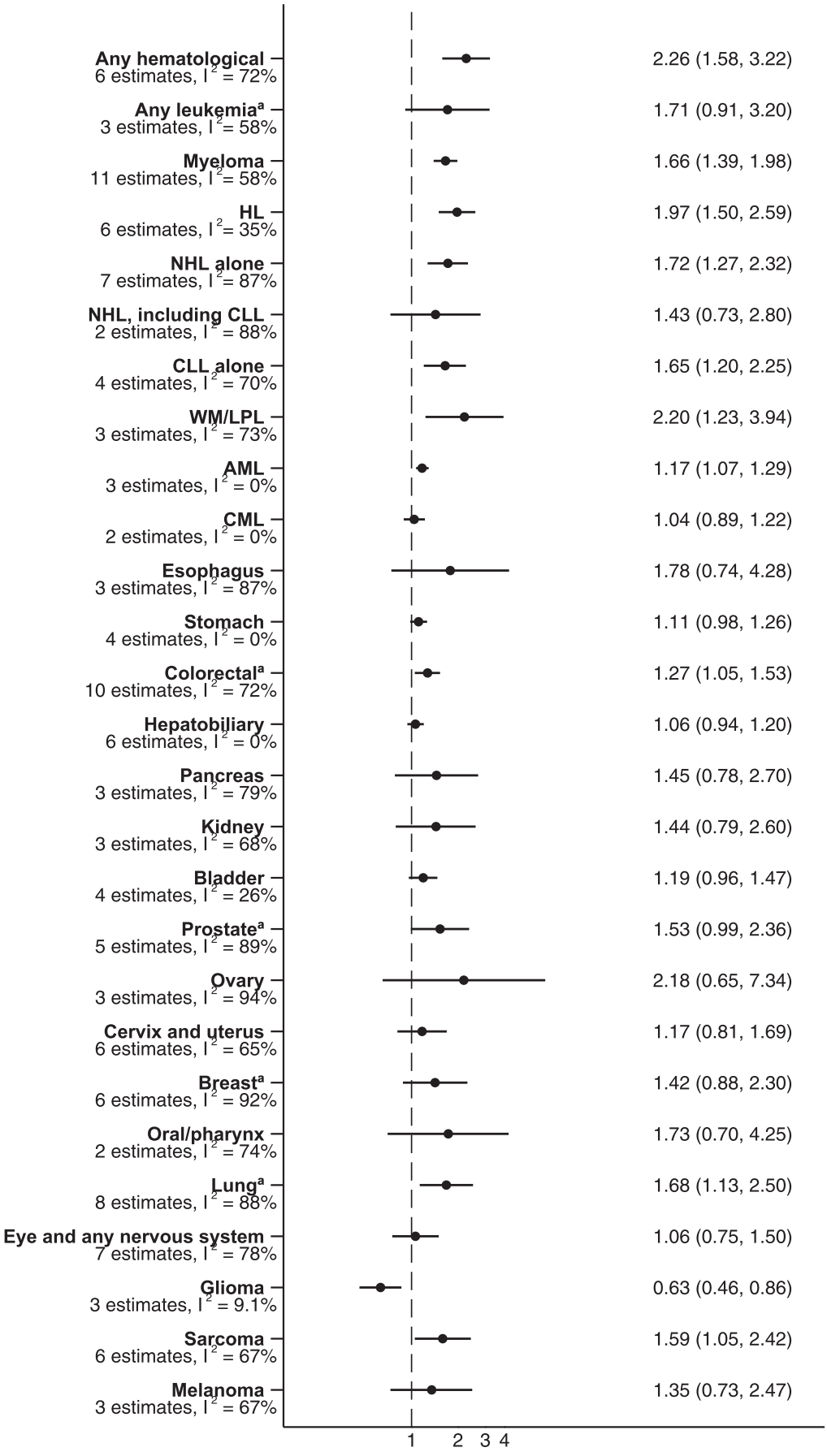


Figure 3 Relative risk estimates (95% confidence intervals) for the association between herpes zoster and subsequent diagnosis of any hematological cancer, ordered according to the magnitude of the effect estimate (several studies reported on multiple subtypes). Notes: The study by Iglar et al. presented estimates for lymphoma and leukemia but was not included in the meta-analysis, as no measure of precision was reported.


Any hematological
6 estimates, I² = 72%
2.26 (1.58, 3.22)
Any leukemia[a]
3 estimates, I² = 58%
1.71 (0.91, 3.20)
Myeloma
11 estimates, I² = 58%
1.66 (1.39, 1.98)
HL
6 estimates, I² = 35%
1.97 (1.50, 2.59)
NHL alone
7 estimates, I² = 87%
1.72 (1.27, 2.32)
NHL, including CLL
2 estimates, I² = 88%
1.43 (0.73, 2.80)
CLL alone
4 estimates, I² = 70%
1.65 (1.20, 2.25)
WM/LPL
3 estimates, I² = 73%
2.20 (1.23, 3.94)
AML
3 estimates, I² = 0%
1.17 (1.07, 1.29)
CML
2 estimates, I² = 0%
1.04 (0.89, 1.22)
Esophagus
3 estimates, I² = 87%
1.78 (0.74, 4.28)
Stomach
4 estimates, I² = 0%
1.11 (0.98, 1.26)
Colorectal[a]
10 estimates, I² = 72%
1.27 (1.05, 1.53)
Hepatobiliary
6 estimates, I² = 0%
1.06 (0.94, 1.20)
Pancreas
3 estimates, I² = 79%
1.45 (0.78, 2.70)
Kidney
3 estimates, I² = 68%
1.44 (0.79, 2.60)
Bladder
4 estimates, I² = 26%
1.19 (0.96, 1.47)
Prostate[a]
5 estimates, I² = 89%
1.53 (0.99, 2.36)
Ovary
3 estimates, I² = 94%
2.18 (0.65, 7.34)
Cervix and uterus
6 estimates, I² = 65%
1.17 (0.81, 1.69)
Breast[a]
6 estimates, I² = 92%
1.42 (0.88, 2.30)
Oral/pharynx
2 estimates, I² = 74%
1.73 (0.70, 4.25)
Lung[a]
8 estimates, I² = 88%
1.68 (1.13, 2.50)
Eye and any nervous system
7 estimates, I² = 78%
1.06 (0.75, 1.50)
Glioma
3 estimates, I² = 9.1%
0.63 (0.46, 0.86)
Sarcoma
6 estimates, I² = 67%
1.59 (1.05, 2.42)
Melanoma
3 estimates, I² = 67%
1.35 (0.73, 2.47)
1
2
3
4

self-reported data, included a representative control group, and did not exclude persons who were dead or too ill for inclusion.

Meta-analyses

The meta-analysis pooling 46 estimates from 34 papers considering any type of hematological cancer yielded a relative risk of 1.60 (95% CI: 1.46, 1.75) (Fig. 3). After restricting to studies with lowest risk of bias, the relative risk was 1.66 (95% CI: 1.47, 1.87) (Web Fig. 2).

Fig. 4 summarizes meta-analyses for individual types of hematological cancer (study-specific estimates are provided in Web Figs. 3 and 4). The pooled estimate for hematological cancers combined was 2.26 (95% CI: 1.58, 3.22). We observed a 40–120% increase in risk of lymphoid hematological cancers, whereas we found lower or neutral estimates for acute myeloid leukemia (1.17, 95% CI: 1.07, 1.29) and chronic myeloid leukemia (1.04, 95% CI: 0.89, 1.22). Parodi et al. similarly reported higher, although statistically very imprecise, effect estimates for myeloid neoplasms (0.55, 95% CI: 0.16, 1.90) than for lymphoid neoplasms (1.80, 95% CI: 0.94, 3.30). These results were not included in the meta-analysis for individual cancers, as the subgroups did not fit into any of the categories.

Most studies on hematological cancer were designed to identify risk factors for cancer and hence deliberately ignored herpes zoster and cancer diagnoses separated by less than 12–13 months (20 studies), 2 years (3 studies), or 5 years (1 study). Considering only studies that included the first year, the pooled relative risk was 1.75 (95% CI: 1.34, 2.29) for all studies on any type of hematological cancer and 2.40 (95% CI: 1.62, 3.55) when further restricting to studies at low risk of bias (Web Fig. 2). Four studies provided estimates for the first year (pooled relative risk 3.52, 95% CI: 2.48, 5.00), but only one was considered at low risk of bias (standardized incidence ratio 3.40, 95% CI: 2.30, 4.90). Most individual studies showed a decrease in relative risk estimates with increasing time since herpes zoster diagnosis (Web Table 5). Even in studies where this pattern was not observed, the relative risk of cancer was increased until 5–10 years after herpes zoster.

Non-hematological cancers

Study characteristics and risk of bias

Seven cohort studies[3–7,45,46] reported on several types of non-hematological cancers (Table 1). We identified additionally five studies on herpes zoster and risk of soft tissue sarcoma or glioma (Table 4).[60,79–82] All five studies were case-control studies judged at high risk of bias (Web Table 4) mainly due to use of self- or proxy-reported data on herpes zoster and exclusion of participants who had died or were too ill to cooperate. Recall bias may be particularly important in the three studies on brain cancer, as the disease process may affect cognitive function.[88]

Meta-analyses

Results for various non-hematological cancers are summarized in Fig. 4. The results from the individual studies contributing data to each meta-analysis are shown in Web Figs. 5–7. Pooled relative risks varied between 0.63 (95% CI: 0.46, 0.86) for glioma and 2.18 (95% CI: 0.65, 7.34) for ovarian cancer. However, the estimate for glioma was based on three small case-control studies at high risk of bias, which contradicted three large cohort studies that considered glioma together with other nervous system tumors.

Besides glioma, the lowest estimate was 1.06 (95% CI: 0.94, 1.20) for hepatobiliary cancers. Only the studies by Sørensen et al. and Iglar et al. reported estimates for cancer diagnosed within one year after herpes zoster (Web Table 5). Overall, the 1 year estimates ranged between 1.0 and 1.2 in both studies, but Sørensen et al. did report higher estimates for selected cancers (sarcoma and cancers of the esophagus, liver and bile ducts, pancreas, kidney, prostate, ovary, and lung), most of which are associated with poor prognosis at time of diagnosis.[89]

Risk of bias across studies

The funnel plots for all studies, studies on overall cancer, cancer diagnosed within one year after herpes zoster, and any type of hematological cancer were not clearly asymmetric (Web Fig. 8).

Discussion

This systematic review shows that herpes zoster may be a marker of occult cancer. Evidence pertaining to subtypes of cancer suggests that a particularly strong association exists between herpes zoster and occult hematological cancer.

One narrative review published in 1995 has previously examined the association between herpes zoster and diagnosis of subsequent malignancy.[25] Based on only two small primary publications from the present review,[43,46] authors of the review concluded that there was no increased cancer risk in patients with herpes zoster.[25] Our review, including 46 papers, does not corroborate the conclusion of the previous review and has several advantages, including a systematic design, a risk of bias assessment and inclusion of more recent evidence on this topic.

Various putative biological mechanisms explaining the association between herpes zoster and cancer have previously been proposed.[3,5] First, carcinogenesis may induce immune deficiency,[90] causing eruption of herpes zoster in the preclinical asymptomatic phase. In particular, hematological cancers may result in depressed

Figure 4 Pooled relative risk estimates (95% confidence intervals) for the association between herpes zoster and subsequent diagnosis of individual types of cancer; Abbreviations: AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; HL = Hodgkin's lymphoma; LPL = lymphoplasmacytic lymphoma; MM = multiple myeloma; NHL = Non-Hodgkin's lymphoma; WM = Waldenström's macroglobulinemia. [a]The study by Iglar et al. also presented estimates for this subtype but was not included in the meta-analysis, as no measure of precision was reported.

number and function of B-cells and T-cells,[90] which accords with the positive association with these cancers. The risk of hematological cancer was increased even at 5—10 years after herpes zoster, which suggests that the immunosuppressive effect may precede cancer diagnosis by several years.[91,92]

Second, cellular immune function is critical both for suppressing varicella-zoster virus replication[1,2,87] and carcinogenesis.[93,94] Herpes zoster could thus be a marker of impaired immunologic surveillance in the host, resulting also in the development of cancer. For example, immune dysregulation in autoimmune diseases may increase the risk of both herpes zoster[87] and some cancers.[95]

Third, it is possible that repetitive antigenic stimulation from subclinical and eventually clinical varicella-zoster virus reactivation causes aggravation of precancerous genetic lesions or triggering of neoplastic transformation.[96,97] Indeed, several human herpesviruses have been implicated directly in oncogenesis through tumor-promoting inflammation, immune evasion, and immunosuppression (e.g., Epstein—Barr virus and risk of Burkitt's lymphoma).[97,98] A direct oncogenic effect of herpes zoster could also explain development of cancer in previous areas affected by herpes zoster.[99—101] However, as the relative risk of cancer decreased with time since herpes zoster, we consider a direct neoplastic effect of herpes zoster the least plausible explanation.

Several limitations of our review should be considered. We devoted particular attention to the risk of cancer diagnosis within the first year after herpes zoster, but this outcome was considered in few studies only. Also, the magnitude of our pooled estimates should be interpreted with caution in light of the large variability between studies in terms of methodology and risk of bias. However, the association was robust when restricting to studies with lowest risk of bias, although statistical heterogeneity remained high.

An increased chance of cancer diagnosis merely due to frequent contact with the healthcare system may possibly explain our results. However, the increased risk of cancer was consistent when comparing studies from different settings (hospital-based versus general practice) and calendar years, and even persisted for several years for some cancer subtypes, which increases our confidence in the findings. Furthermore, studies presenting estimates according to follow-up periods showed no compensatory drop in the number of cancers following the initial increase.

While immunological studies support an immunosuppressive effect of tobacco[102] and alcohol,[103] studies on the effect of smoking and drinking habits on risk of herpes zoster are conflicting.[87,104,105] It is therefore difficult to predict if an increased prevalence of such health-related behaviors can explain the increased risk of occult cancer. However, we note that the effect estimates were not particularly pronounced for smoking- or alcohol-related cancers.

We aimed to identify pertinent studies using a broad search strategy and our funnel plots showed no strong evidence of small study bias, thus arguing against publication bias. Nevertheless, we may have missed studies that examined a wide range of exposures as risk factors for cancer, if herpes zoster was not mentioned explicitly in the title, abstract, or key words. Selective outcome reporting, in particular in studies considering multiple predictors and cancer subtypes, is also a potential threat to the validity of our review. Conversely, multiplicative reports occurred frequently. Notably, there were four Taiwanese studies examining the association between herpes zoster and subsequent cancer using the same database.[5,30,40,70] We were unable to retrieve the full-text article of two non-English studies.[9,26] Based on the abstract, the Japanese study was a cross-sectional study of 220 hospitalized herpes zoster patients, among whom cancer was detected in 4 persons during the hospital stay compared with 0.27 expected.[9] Thus, exclusion of the study is unlikely to have affected our conclusion. However, the case-control study from Iran, which included 268 cases and 268 cancer-free controls, found an odds ratio of 0.44 (95% CI: 0.22, 0.86) for self-reported history of herpes zoster.[26]

Some authors have argued in favor of increased awareness of underlying cancer in herpes zoster patients,[3,8,9] whereas others have taken a more precautious stand.[4,7,43,44,46] We agree with the latter view for several reasons. Although we showed a higher risk of cancer in this review, only few studies reported absolute risks and risk differences. Based on the studies conducted in the general population, we estimated that the risk of cancer within one year after herpes zoster was only about 0.7%—1.1%. Furthermore, none of the studies investigated whether the increased risk of occult cancer depended on the presence of classic risk factors for herpes zoster, e.g., use of immunosuppressive drugs. Such information could have important implications for targeting work-up strategies at certain high-risk groups. Finally, our literature search revealed a lack of studies on benefits and harms of extensive work-up for cancer in herpes zoster patients. It is possible that detection of some occult cancers requires extensive, costly and stressful diagnostic procedures, without any appreciable effect on prognosis. These present gaps in literature thus preclude us from formulating guidelines with profound consequences for current clinical practice.

In conclusion, this systematic review shows evidence of an association between herpes zoster and occult cancer. We detected a particularly high relative risk for hematological cancers. Our study was limited by large between-study heterogeneity, which complicates accurate quantification of the association. Furthermore, few studies reported data on absolute measures of risk and we found no studies on the effect of extensive diagnostic work-up on cancer outcome. Thus, although the association between herpes zoster and cancer is intriguing, the clinical implications remain unclear.

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Contributors' statement

SAJS conceived the study idea. All authors contributed to study concept and design. SAJS performed the literature search and initial screening. SAJS and AM performed

eligibility screening and data extraction. SAJS carried out the data analysis. All authors participated in the discussion and interpretation of the results. SAJS wrote the initial manuscript draft. All authors critically revised the manuscript for intellectual content and approved the final version. SAJS is the guarantor.

Conflict of interest

The authors declare no conflict of interest. Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies have relation to the present study. The study funder had no control over the planning, interpretation, writing, or publication of this work.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jinf.2016.11.005.

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WEB MATERIAL

Contents

Web Methods 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, Web Methods 3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, Web Methods 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4–5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4–5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4–5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5–6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Web Methods 2 Meta-Analyses of Observational Studies in Epidemiology (MOOSE) checklist

Checklist item	Reported on page	Comments
Reporting of background should include		
Problem definition	3	
Hypothesis statement	3	
Description of study outcomes	3	Last paragraph of introduction lists cancer as the outcome, and also specifies the primary and secondary aims.
Type of exposure or intervention used	3–4	Herpes zoster is specified as the exposure/predictor of interest in both the background section and the description of eligibility criteria.
Type of study designs used	3–4	No restriction as long a control group was included, as specified in the last paragraph of the introduction and the eligibility criteria
Study population	3–4	No restriction as long a control group was included, as specified in the eligibility criteria
Reporting of search strategy should include		
Qualifications of searchers (eg librarians and investigators)	4	
Search strategy, including time period used in the synthesis and key words	4, Web Methods 3	
Effort to include all available studies, including contact with authors	5	
Databases and registries searched	4, Web Methods 3	
Search software used, name and version, including special features used (eg explosion)	4, Web Methods 3	
Use of hand searching (eg reference lists of obtained articles)	4, Web Methods 3	
List of citations located and those excluded, including justification	7, Web Table 1	Results section about systematic literature search and Web Table 1.
Method of addressing articles published in languages other than English	4	
Method of handling abstracts and unpublished studies	4	
Description of any contact with authors	5	Estimates provided by authors are marked in tables.
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5	Risk of bias assessment
Rationale for the selection and coding of data (eg sound clinical principles or convenience)	4–5	Use of piloted form and to reviewers described in methods section
Documentation of how data were classified and coded (eg multiple raters, blinding and interrater reliability)	4–5, 7, Web Table 2	Use of piloted form and two reviewers described in methods section. Disagreements between reviewers described in Web Table 2.
Assessment of confounding (eg comparability of cases and controls in studies where appropriate)	5	Described in section about risk of bias assessment
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	5–6	Risk of bias assessment describes methodological characteristics considered and Statistical

		Analysis sensitivity analyses performed to assess their impact on results.
Assessment of heterogeneity	6	Statistical heterogeneity described in Statistical Analysis section
Description of statistical methods (eg complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6–7	
Provision of appropriate tables and graphics	Tables and Figures in main text and Supplementary Appendix	
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Figures 2–4 and Web Material	Individual estimates forming basis for Figure 4 are shown in the Web Material together with other additional data.
Table giving descriptive information for each study included	Tables 1, 3, 5	
Results of sensitivity testing (eg subgroup analysis)	Figure 2, Web Figure 2	
Indication of statistical uncertainty of findings	Figures	Statistical uncertainty indicated by use of confidence intervals
Reporting of discussion should include		
Quantitative assessment of bias (eg publication bias)	Web Figure 8	
Justification for exclusion (eg exclusion of non-English language citations)	Figure 1, Web Table 1	Flowchart showing selection process. Two non-English studies excluded because full-text was not available. One non-English study was assessed but excluded due to ineligibility.
Assessment of quality of included studies	8–9, 11, 13, Web Table 4	Described in detail in main text for studies on overall cancer. Summarized in main text for studies on individual cancers, with more details in Web Table 4.
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	14–16	Potential biological explanations and biases are described in the discussion.
Generalization of the conclusions (eg appropriate for the data presented and within the domain of the literature review)	16–17	Discussion of reporting biases and generalizability to various types of herpes zoster patients.
Guidelines for future research	16–17	The lack of data on absolute risk of cancer, risk of cancer in subgroups of herpes zoster patients, and the utility of diagnostic work-up is discussed.
Disclosure of funding source	17	

Web Methods 3. Search strategy

Electronic search of MEDLINE (PubMed) and EMBASE was performed, with the last date searched February 1, 2015. The search string used is outlines in detail below. Reference lists of eligible papers were also hand-searched to identify further relevant studies. An updated search was performed February 18, 2016.

a. MEDLINE (PubMed) search strategy
Searching with automatic mapping

1. zoster
2. shingles
3. #1 OR #2
4. "Neoplasms"[Mesh]
5. cancer*[Title]
6. malignan*[Title]
7. neoplas*[Title]
8. tumo*[Title]
9. carcinoma*[Title]
10. sarcoma*[Title]
11. lymphoma*[Title] OR hodgkin*[Title]
12. leukemia*[Title] OR leukaemia*[Title]
13. myeloma*[Title]
14. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
15. risk
16. incidence
17. #15 OR #16
18. #3 AND #14 AND #17

b. EMBASE.com search strategy
Searching as broadly as possible, including map, explode, and free text in all fields unless otherwise specified.

1. 'herpes zoster'/syn
2. cancer*:ti
3. malignan*:ti
4. neoplas*:ti
5. tumo*:ti
6. carcinoma*:ti
7. sarcoma*:ti
8. lymphoma*:ti OR hogkin*:ti
9. leukemia*:ti OR leukaemia*:ti
10. myeloma*:ti
11. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. 'risk'/syn
13. 'incidence'/syn
14. 'cancer incidence'/syn
15. #12 OR #13 OR #14
16. #1 AND #11 AND #15

Web Table 1. Characteristics of excluded studies

Study	Reason for exclusion
Completely excluded studies	
Bernard SM, 1987[1]	Overlap with included study by McKinney *et al* (1990).
Buntinx F, 2005[2]	Overlap with an updated study from 2014 by the same author, which was included instead.
Franceschi S, 1989[3]	Overlap with included multicenter study by Becker *et al* (2012).
Ho J-D, 2011[4]	Overlap with included study by Chiu *et al* (2013), but considers herpes zoster ophthalmicus only.
Holly EA, 2003[5]	Overlap with included study by Becker *et al* (Int J Cancer, 2012).
Karunanayake CP, 2009[6]	Overlap with included studies by Pahwa *et al* (2012) and Karunanayake *et al* (2012).
Maia R, 2013[7]	Review of the association between infections and childhood leukemia. Herpes zoster not included.
McKinney PA, 1990[8]	Overlap with included study by McKinney *et al* (1990).
Molin L, 1975[9]	No comparison group.
Nassaji M, 2016[10]	Iranian study for which we were unable to retrieve the full-text.
Newton R, 2007[11]	Studied chickenpox and zoster together.
Pahwa P, 2009[12]	Overlap with included studies by Pahwa *et al* (2012) and Karunanayake *et al.* (2012).
Pahwa P, 2003[13]	Overlap with included studies by Pahwa *et al* (2012) and Karunanayake *et al.* (2012), but restricted to farm residents.
Serraino D, 1991a[14]	Overlap with included study by Tavani *et al* (2000), which has longer study period.
Serraino D, 1991b[15]	Overlap with included study by Franceschi *et al* (1992), which has longer study period.
Sheu J-J, 2012[16]	Considered Bell's palsy, not herpes zoster.
Smith JB, 1995[17]	Narrative review.
Vajdic CM, 2006[18]	Overlap with included study by Becker *et al* (2012).
Viadana E, 1974[19]	Overlap with included study by Gibson *et al* (2016). Although the study by Gibson *et al* comprised men only, it was included in the review because definition of previous herpes zoster was less restrictive (ignored herpes zoster within one year before index date rather than five years).
Vineis P, 2000[20]	Data on the 1388 NHL cases overlapped with the included multicenter study by Becker *et al* (2012). Although other subtypes of hematological cancer were included, authors did not provide any results because there were less than 5 exposed cases.
Wang Y-P, 2012[21]	Overlap with included study by Chiu *et al* (2013).
Wrensch M, 1997[22]	Examined chickenpox with focus on serology.
Zaha M, 1993[23]	Japanese study for which we were unable to retrieve the full-text.
Zhang Y, 2004[24]	Overlap with included multicenter study by Becker *et al* (2012).
Partly excluded studies	
Cartwright RA, 1988[25]	The included study by McKinney *et al* (1990) published in Leuk Lymphoma reported overlapping data on NHL and reported also data on other cancer types, which we included. However, for NHL in particular we used data from this study by Cartwright *et al*, as they did not exclude early cancers, which was the main interest of the review.
Cartwright RA, 1987[26]	The included study by McKinney *et al* (1990) published in Leuk Lymphoma reported overlapping data on CLL and reported also data on other cancer types, which we included. However, for CLL in particular we used data from this study by Cartwright *et al*, as they did not exclude early cancers, which was the main interest of the review.
Chiu H-F, 2013[27]	This study was included in the assessment of evidence for any cancer and non-hematological cancers. Data on hematological cancers was not presented separately. However, a study by Liu *et al* (2013)

	included data on hematological cancer specifically, which we included in the review of studies on this cancer type.
Liu Y-C, 2012[28]	Overlap with study by Chiu *et al* (2013), which was included for any cancer and non-hematological cancers. However, the study by Liu *et al* included data on hematological cancer specifically, which we included in the review of studies on this cancer type.
Mahale P, 2016[29]	The studies by Anderson *et al* (2014), Anderson *et al* (2009), McShane *et al* (*Br J Haematol*, 2014), McShane *et al* (*Int J Cancer*, 2014) and Titmarsh *et al* (2014) reported more comprehensive data for, which we included in the review. However, data on non-hematological cancer were included from this study by Mahale *et al.*
McKinney PA, 1990[30]	The two studies by Cartwright *et al* (1987; 1988) reported more comprehensive data for NHL and CLL, which we included in the review. However, data on other subtypes of hematological cancer (HL, CML, ALL and AML) were included from this study by McKinney *et al.*
Tavani A, 2000[31]	Overlap with data on NHL from the multicenter study by Becker *et al* (2012). However, this study by Tavani *et al* included also 158 HL cases, which we included in the review.

Abbreviations: CML=chronic myeloid leukemia; CLL=chronic lymphocytic leukemia; NHL=non-Hodgkin's lymphoma; ALL=acute lymphocytic leukemia; AML=acute myeloid leukemia

References to table

1 Bernard SM, Cartwright RA, Darwin CM, *et al.* Hodgkin's disease: case control epidemiological study in Yorkshire. *Br J Cancer* 1987; **55**: 85–90.

2 Buntinx F, Wachana R, Bartholomeeusen S, Sweldens K, Geys H. Is herpes zoster a marker for occult or subsequent malignancy? *Br J Gen Pract* 2005; **55**: 102–7.

3 Franceschi S, Serraino D, Bidoli E, *et al.* The epidemiology of non-Hodgkin's lymphoma in the north-east of Italy: a hospital-based case-control study. *Leuk Res* 1989; **13**: 465–72.

4 Ho JD, Xirasagar S, Lin HC. Increased risk of a cancer diagnosis after herpes zoster ophthalmicus: a nationwide population-based study. *Ophthalmology* 2011; **118**: 1076–81.

5 Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. *Am J Epidemiol* 2003.

6 Karunanayake CP, Singh GV, Spinelli JJ, *et al.* Occupational exposures and Hodgkin Lymphoma: Canadian case-control study. *J Occup Environ Med* 2009; **51**: 1447–54.

7 Maia R, Filho VW. Infection and childhood leukemia: review of evidence. *Revista de saude publica* 2013.

8 McKinney PA, Roberts BE, O'Brien C, *et al.* Chronic myeloid leukaemia in Yorkshire: a case control study. *Acta Haematol* 1990; **83**: 35–8.

9 Molin L. [Is zoster a sign of undiagnosed cancer?]. *Lakartidningen* 1975; **72**: 1087–8.

10 Nassaji M, Ghahramanfard F, Jahanbanifar M, Ghorbani R. Is herpes zoster a risk factor for subsequent malignancy? *Koomesh* 2016; **17**: Pe486–92, En57.

11 Newton R, Crouch S, Ansell P, *et al.* Hodgkin's lymphoma and infection: findings from a UK case-control study. *Br J Cancer* 2007; **97**: 1310–4.

12 Pahwa P, Karunanayake CP, Spinelli JJ, Dosman JA, McDuffie HH. Ethnicity and incidence of Hodgkin lymphoma in Canadian population. *BMC Cancer* 2009; **9**: 141.

13 Pahwa P, McDuffie HH, Dosman JA, *et al.* Exposure to animals and selected risk factors among Canadian

farm residents with Hodgkin's disease, multiple myeloma, or soft tissue sarcoma. *J Occup Environ Med* 2003; **45**: 857–68.

14 Serraino D, Franceschi S, Talamini R, *et al.* Socio-economic indicators, infectious diseases and Hodgkin's disease. *Int J Cancer* 1991; **47**: 352–7.

15 Serraino D, Franceschi S, Talamini R, Frustaci S, La Vecchia C. Non-occupational risk factors for adult soft-tissue sarcoma in northern Italy. *Cancer Causes Control* 1991; **2**: 157–64.

16 Sheu J-J, Keller JJ, Lin HC. Increased risk of cancer after Bell's palsy: a 5-year follow-up study. *J Neurooncol* 2012; **110**: 215–20.

17 Smith JB, Fenske NA. Herpes zoster and internal malignancy. *South Med J* 1995; **88**: 1089–92.

18 Vajdic CM, Grulich AE, Kaldor JM, *et al.* Specific infections, infection-related behavior, and risk of non-Hodgkin lymphoma in adults. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 1102–8.

19 Viadana E, Bross ID. Use of the medical history to predict the future occurrence of leukemias in adults. *Prev Med* 1974; **3**: 165–70.

20 Vineis P, Crosignani P, Sacerdote C, *et al.* Haematopoietic cancer and medical history: a multicentre case control study. *J Epidemiol Community Health* 2000; **54**: 431–6.

21 Wang YP, Liu CJ, Hu YW, Chen TJ, Lin YT, Fung CP. Risk of cancer among patients with herpes zoster infection: a population-based study. *CMAJ* 2012; **184**: E804–9.

22 Wrensch M, Weinberg A, Wiencke J, *et al.* Does prior infection with varicella-zoster virus influence risk of adult glioma? *Am J Epidemiol* 1997; **145**: 594–7.

23 Zaha M, Hayashi I, Odashiro M, *et al.* [Herpes zoster and malignancy]. *Masui* 1993; **42**: 1343–6.

24 Zhang Y, Holford TR, Leaderer B, *et al.* Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. *Cancer Causes Control* 2004; **15**: 419–28.

25 Cartwright RA, McKinney PA, O'Brien C, *et al.* Non-Hodgkin's lymphoma: case control epidemiological study in Yorkshire. *Leuk Res* 1988; **12**: 81–8.

26 Cartwright RA, Bernard SM, Bird CC, *et al.* Chronic lymphocytic leukaemia: case control epidemiological study in Yorkshire. *Br J Cancer* 1987; **56**: 79–82.

27 Chiu H-F, Chen BK, Yang C-Y. Herpes zoster and subsequent risk of cancer: a population-based study. *Journal of Epidemiology* 2013; **23**: 205.

28 Liu Y-C, Yang Y-H, Hsiao H-H, *et al.* Herpes zoster is associated with an increased risk of subsequent lymphoid malignancies - a nationwide population-based matched-control study in Taiwan. *BMC Cancer* 2012; **12**: 503.

29 Mahale P, Yanik EL, Engels EA. Herpes Zoster and Risk of Cancer in the Elderly U.S. Population. *Cancer Epidemiol Biomarkers Prev* 2016; **25**: 28–35.

30 McKinney PA, Alexander FE, Roberts BE, O'Brien C, Bird CC, Cartwright RA. Yorkshire case control study of leukaemias and lymphomas parallel multivariate analyses of seven disease categories. *Leuk Lymphoma* 1990; **2**: 67–80.

31 Tavani A, La Vecchia C, Franceschi S, Serraino D, Carbone A. Medical history and risk of Hodgkin‘s and non-Hodgkin’s lymphomas. *Eur J Cancer Prev* 2000; **9**: 59–64.

Web Table 2. Disagreements between reviewers during eligibility assessment of in total 69 studies

Author	Decision about eligibility		
	Reviewer 1	Reviewer 2	Consensus
Guess HA, 1985	Include	Exclude – no comparison group	Include, because re-evaluation of the study showed that authors reported incidence ratios standardized to the general population.
Maia R, 2013	Exclude – study is a review on infections and childhood leukemia, and none of the included studies examined herpes zoster specifically	Include	Exclude, because it is a review of the association between infections and childhood leukemia. Herpes zoster not included.
Molin L, 1975	Exclude – no comparison group	Include	Exclude, because re-evaluation of the study (which was in Swedish) showed that no comparison group without herpes zoster was included.
Newton R, 2007	Exclude –chickenpox and zoster were considered together	Include	Exclude, because chickenpox was also included in the estimate for herpes zoster, which limits comparability with other studies included.
Sheu J-J, 2012	Exclude – considered only Bell's palsy	Include	Exclude, because Bell's palsy is defined as one-sided facial paralysis of unknown cause, and may thus have other underlying causes than herpes zoster.

Note: There was agreement for the remaining 64 studies.

Web Table 3. Association between herpes zoster and subsequent diagnosis of cancer, by time between diagnoses

Lead author, year	Relative risk estimate (95% CI)
Buntinx F, 2014	Women: - 2.11 (1.15 to 3.87) within first year - 1.60 (1.21 to 2.11) overall Men: N.R., likely because of statistical insignificance
Chiu H-F, 2013	- 2.18 (1.93 to 2.46) within first year - 1.58 (1.38 to 1.80) within first year, excluding first two months - 1.30 (1.15 to 1.46) between first and second year - 1.10 (0.98 to 1.24) between second and third year - 1.02 (0.91 to 1.15) between third and fourth year - 1.08 (0.96 to 1.21) between fourth to fifth year
Cotton SJ, 2013	- 20.5 (10.4 to 40.8) at 90 days - 9.4 (6.5 to 13.7) at 180 days - 4.4 (3.6 to 5.5) at 1 year - 2.9 (2.5 to 3.3) at 3 years - 2.4 (2.2 to 2.7) at 5 years
Iglar K, 2013	- 1.19 (1.12 to 1.25) at 180 days - 1.11 (1.00 to 1.19) at 1 year - 1.11 (1.08 to 1.15) at 2 years - 1.10 (1.07 to 1.12) at 3 years - 1.09 (1.07 to 1.11) at 4 years - 1.08 (1.06 to 1.10) at 5 years
Ragozzino MW, 1982	- 1.0 (0.3 to 2.6) within first year - 0.9 (0.5 to 1.5) within second through fifth year - 1.1 (0.9 to 1.4) after fifth year
Sørensen HT, 2004	- 1.3 (1.1 to 1.5) within first year, excluding first two months of follow-up - 1.1 (1.1 to 1.2) after first year
Yamamoto M, 2003	- No cancers observed within the first year. However, among 131 patients who received work-up for cancer at admission, 6 had occult cancer, which was significantly higher than the expected number (CI: N.R.) based on cancer incidence in background population. - 2.07 (CI: N.R.) within first through fifth year - 1.35 (CI: N.R.) after fifth year

Abbreviations: CI=confidence interval; HR=hazard ratio; N.R.=Not reported; SIR=standardized incidence ratio

Web Table 4. Risk of bias in included studies on herpes zoster and cancer subtypes

First author, year	Main risk of bias in study
Amadori D, 1995	- Differential participation. 12% of cases refused to cooperate or died before inclusion. - Recall bias, as HZ was self-reported or proxy-reported (by *e.g.* next of kin).
Anderson LA, 2014	- Misclassification of exposure possible as NHL cases had longer (less left-censoring) and HL cases had shorter (more left-censoring) duration of Medicare coverage than their controls. - Treatment outside the Medicare system may have resulted in misclassification of exposure or outcome.
Anderson LA, 2009	- Misclassification of exposure is possible, as cases had longer Medicare coverage (less left-censoring) than controls. - Treatment outside the Medicare system may have resulted in misclassification of exposure or outcome.
Andreotti G, 2015	- Differential participation. 49% of cases were not included because they were deceased, impossible to tract etc. Among cases, 72% had a spouse and response rate for spouses was estimated at 51%. - Exposure prevalence in spouses may not reflect the exposure prevalence in the source population, because direct contact with a person with active herpes zoster may theoretically boosts the varicella-zoster-specific immunity and thereby decrease the risk of contracting herpes zoster. - Recall bias, as HZ was self-reported.
Becker N, 2012	- Differential participation. Response rate in included centers varied between 65% to 97% among cases and 44% to 99% among controls. - Many of the included centers used hospital controls, who may not be representative of the source population. - Recall bias, as HZ was self-reported.
Bernstein L, 1992	- Differential participation. 55% of cases had died, were too ill for interview, refused to participate, were untraceable, had moved from the county, or because the physician denied contact. On average, 21 household units were contacted to identify a consenting matched neighborhood control. - Recall bias, as HZ was self-reported. - Lack of control for age and sex, as only crude results are presented. Authors matched by birth year, race and sex in the design phase of the study, but matching was not accounted for in analyses.
Brown LM, 2008	- Treatment outside the VA system (e.g. at Civilian facilities, Medicare) could result in lack of systematic follow-up and misclassification of exposure or outcome.
Cartwright RA, 1988	- Differential participation. 58% cases were not included due to death, refusal, emigration, language problems, severe symptoms etc. - Use of hospital controls, who may not be representative of the source population. - Recall bias, as HZ was self- or proxy-reported (by *e.g.* next of kin). However, authors did verify against records for accuracy.
Cartwright RA, 1987	- Differential participation. 20% of cases <70 years and approx. 50% of cases ≥70 years were excluded. Excluded cases tended to come from distant parts of the region and most had died before inclusion. - Use of hospital controls, who may not be representative of the source population. - Recall bias, as HZ was self- or proxy-reported (by *e.g.* next of kin). However, authors did verify against records for accuracy.
Cuzick J, 1988	- Differential participation, but proportion not reported. - Use of hospital controls, who may not be representative of the source population. Authors state that GP controls were also available for analysis (260 matched pairs) but there was no difference between these data and the analysis using hospital controls. - Recall bias, as HZ was self-reported. However, authors aimed to verify against records when possible. - Lack of control for age and sex, as only crude results are presented. Authors matched by age and sex in the design phase of the study, but matching was not accounted for in analyses.
Doody MM, 1992	- Differential participation. 12% of cases were excluded due to lack of matched controls and 21% were excluded because they had been program members for <5 years before diagnosis. - Lack of control for age and sex, as only crude results are presented. Authors matched by age, sex, number of years in program, and calendar year for membership start in the design phase of the study, but matching was not accounted for in analyses.
Franceschi S, 1992	- Differential participation. Up to 2 years could have passed between cancer diagnosis and inclusion, possibly resulting in exclusion of persons with aggressive cancer. - Use of hospital controls, who may not be representative of the source population. - Recall bias, as HZ was self-reported.
Gibson R, 1976	- Differential participation. 28% of cases were excluded because neither patient nor spouse respondent was available. - Recall bias, as HZ was self- or proxy-reported (by *e.g.* next of kin). Only 8% of acute leukemia cases and 36% of chronic leukemia cases were alive for interview compared with 98% of controls. Authors aimed to test the accuracy of information through re-interviews, recoding, blinded interviewing, and use of hospital controls instead of general population controls, which revealed similar results.
Gramenzi A, 1991	- Differential participation. Up to 1 year could have passed between cancer diagnosis and inclusion, possibly resulting in exclusion of persons with persons with aggressive cancer. - Use of hospital controls, who may not be representative of the source population. - Recall bias, as HZ was self-reported.

First author, year	Main risk of bias in study
Karunanayake CP, 2012	- Differential participation. 32% of contacted HL cases, 39% of contacted STS cases, 32.9% of NHL cases, and 52% of all contacted controls were excluded for various reasons, including death, change of address, and refusal. - Recall bias, as HZ was self-reported.
Koepsell CP, 1987	- Differential participation. 11% of eligible cases and 17% of controls were excluded for various reasons, including physician refusal, patient refusal, emigration from study region, language difficulty etc. - Recall bias, as HZ was self- or proxy-reported (by *e.g.* next of kin). 32% of cases and 1% of controls had interviews performed in spouse or relative (due to death or illness of cases). Estimates were higher when restricting to self-respondents only, indicating underreporting by proxies.
Koshiol J, 2011	- Treatment outside the VA system (e.g. at Civilian facilities, Medicare) could result in lack of systematic follow-up and misclassification of exposure or outcome.
Koshiol J, 2008	- Treatment outside the VA system (e.g. at Civilian facilities, Medicare) could result in lack of systematic follow-up and misclassification of exposure or outcome.
Kristinsson SY, 2015	- Included only hospital-diagnosed HZ, which would at most probably give bias toward the null. However, it could affect generalizability if severe HZ is more strongly associated with cancer.
Kristinsson SY, 2011	- Included only hospital-diagnosed HZ, which would at most probably give bias toward the null. However, it could affect generalizability if severe HZ is more strongly associated with cancer.
Kristinsson SY, 2010	- Included only hospital-diagnosed HZ, which would at most probably give bias toward the null. However, it could affect generalizability if severe HZ is more strongly associated with cancer.
Landgren O, 2007	- Treatment outside the VA system (e.g. at Civilian facilities, Medicare) could result in lack of systematic follow-up and misclassification of exposure or outcome.
La Vecchia C, 1992	- Differential participation. Up to 1 year could have passed between cancer diagnosis and inclusion, possibly resulting in exclusion of persons with aggressive cancer. - Use of hospital controls, who may not be representative of the source population. - Recall bias, as HZ was self-reported.
Lewis DR, 1994	- Differential participation. 37% of cases were excluded for various reasons, including because they had died, were too ill for interview, refused to participate, had language difficulty, or because the physician denied contact. The response prevalence among controls was 67% for random digit dialing and 22 to 23% for controls for Medicare files. - Recall bias, as HZ was self-reported.
Liu Y-C, 2012	- Lack of systematic follow-up and potential misclassification of exposure and outcome because the database relies on insurance claims. However, the vast majority in the population is insured.
McKinney PA, 1990	- Differential participation. 45 to 50% of cases were excluded for various reasons, including death, refusal, emigration, language problems etc. - Use of hospital controls, who may not be representative of the source population. - Recall bias, as HZ was self-reported. However, authors verified against records for accuracy.
McShane CM, *Br J Haematol,* 2014	- Misclassification of exposure possible, as cases had longer Medicare coverage (less left-censoring) than controls. - Treatment outside the Medicare system may have resulted in misclassification of exposure or outcome.
McShane CM, *Int J Cancer,* 2014	- Misclassification of exposure possible, as cases had longer Medicare coverage (less left-censoring) than controls. - Treatment outside the Medicare system may have resulted in misclassification of exposure or outcome.
Nanni O, 1998	- Differential participation, as some patients may have refused to cooperate or died. - Recall bias, as HZ was self- or proxy-reported (by *e.g.* next of kin).
Pahwa P, 2012	- Differential participation. 42% of cases and 52% of controls were excluded due death, change of address, refusal etc. - Recall bias, as HZ was self-reported.
Parodi S, 2012	- Differential participation. 53% of cases were excluded for various reasons, including death and because only proxies were available for interview. - Recall bias, as HZ was self-reported.
Scheurer ME, 2008	- Differential participation, as 23% of cases and 47% of controls were excluded due to non-response. - Recall bias
Tavani A, 2000	- Differential participation. Only those who survived up to 2 years after cancer diagnosis were included, possibly resulting in exclusion of persons with aggressive cancer. - Use of hospital controls, who may not be representative of the source population. - Recall bias, as HZ was self-reported.
Titmarsh GJ, 2014	- Misclassification of exposure possible, as cases had longer Medicare coverage (less left-censoring) than controls. - Treatment outside the Medicare system may have resulted in misclassification of exposure or outcome.
Wrench M, 1997	- Differential participation. 18% of cases were excluded due to decline, physician refusal, or because authors were unable to locate cases or suitable proxies. Nonparticipants were more likely to be male and older, which may be associated with aggressiveness of tumor and thus selection bias. - Recall bias, as HZ was self- or proxy-reported (by *e.g.* next of kin). 46% of cases had proxy interviews. However, estimate did not differ for self-report and proxy-report.
Wrench M, 2005	- Differential participation. 21% of cases identified were excluded due to decline, physician refusal, or because authors were unable to locate cases/suitable proxies. 26% of eligible controls were excluded.

First author, year	Main risk of bias in study
	- Recall bias, as HZ was self- or proxy-reported (by *e.g.* next of kin). 33% of cases had proxy interviews. However, estimate did not differ for self-report and proxy-report.

Abbreviations: HL=Hodgkin's lymphoma; HZ=herpes zoster, NHL= Non-Hodgkin's lymphoma; VA=Veterans Affairs

Web Table 5. Association between herpes zoster and subsequent diagnosis of individual types of cancer, by time between diagnoses

	Relative risk estimate (95% confidence intervals)
Overall haematological malignancy	
Parodi S, 2012	- 1.46 (0.018 to 115.19) at 1 year[a]
Sørensen HT, 2004	- 3.4 (2.3 to 4.9) at 1 year - 1.7 (1.4 to 2.0) thereafter
Lymphoid haematological malignancy	
Parodi S, 2012	- 1.8 (0.94 to 3.3) overall[a] - 1.7 (0.84 to 3.4) when using a 5-year lag period
Myeloid haematological malignancy	
Parodi S, 2012	- 0.55 (0.16 to 1.9) overall[a] - 0.69 (0.19 to 2.4) when using a 5-year lag period
Lymphoma overall	
Iglar K, 2013	- 2.12 (CI: N.R.) at 180 days - 1.94 (CI: N.R.) at 1 year - 1.65 (CI: N.R.) at 2 years - 1.51 (CI: N.R.) at 3 years - 1.51 (CI: N.R.) at 4 years - 1.46 (CI: N.R.) at 5 years
Leukaemia overall	
Iglar K, 2013	- 1.59 (CI: N.R.) at 180 days - 1.42 (CI: N.R.) at 1 year - 1.43 (CI: N.R.) at 2 years - 1.41 (CI: N.R.) at 3 years - 1.39 (CI: N.R.) at 4 years - 1.35 (CI: N.R.) at 5 years
Sørensen HT, 2004	- 2.8 (1.3 to 5.1) at 1 year - 1.7 (1.2 to 2.2) thereafter
NHL (excluding CLL)	
Anderson LA, 2014	- 1.29 (1.19 to 1.40) for 13–30 months - 1.36 (1.24 to 1.49) for 31–48 months - 1.24 (1.13 to 1.36) for 49–72 months - 1.24 (1.13 to 1.37) for >72 months
Cartwright RA, 1988	- 8.5 (1.4 to 51.2) for 0–1 year - 5.1 (1.1 to 14.3) for 2–4 years - 2.4 (1.1 to 5.3) for 5–9 years - 1.9 (1.0 to 3.9) for 10–14 years - 1.9 (1.0 to 3.9) for 15+ years
Koshiol J, 2011	- 3.86 (2.75 to 5.42) for 2–4 years - 1.75 (1.10 to 2.78) for 5–9 years - 1.61 (1.13 to 2.31) for ≥10 years[a]
La Vecchia C, 1992	- 7.0 (2.0 to 25.0) for 1–10 years before - 2.0 (1.1 to 4.0) for ≥10 years before
Sørensen HT, 2004	- 3.8 (1.9 to 6.7) at 1 year - 1.6 (1.1 to 2.2) thereafter
NHL (including CLL)	
Amadori D, 1995	- 2.34 (1.20 to 4.57) for 2–10 years - 1.95 (1.11 to 3.41) for >10 years
CLL	
Anderson LA, 2009	- 1.70 (1.48 to 1.94) for 13–30 months - 1.50 (1.28 to 1.76) for 31–48 months - 1.37 (1.16 to 1.60) for 49–72 months - 1.18 (0.98 to 1.41) for >72 months[a]
Cartwright RA, 1987	- 3.6 (1.2 to 11.2) for 0–1 y - 2.4 (0.9 to 6.7) for 2–4 y - 1.3 (0.7 to 2.5) for ≥5 y
Landgren O, 2007	- 2.37 (1.18 to 4.75) for 2–4 years - 1.52 (0.72 to 3.20) for 5–9 years - 2.07 (1.30 to 3.29) for ≥10 years[a]
WM-LL	
Kristinsson SY, 2010	- 4.2 (2.0 to 8.8) for 1–5 years - 2.5 (1.2 to 5.2) for >5 years
McShane CM, *Br J Haematol*, 2014	- 1.22 (0.67 to 2.23) for 13–30 months - 1.13 (0.56 to 2.28) for 31–48 months - 1.93 (1.15 to 3.23) for 49–72 months

	- 1.79 (1.03 to 3.12) for >72 months
AML	
Kristinsson SY, 2011	- 1.1 (0.7 to 1.7) for >1 year - 1.2 (0.8 to 2.1) for >3 years
Titmarsh GJ, 2014	- 1.30 (1.10 to 1.54) for 13–30 months - 1.19 (0.98 to 1.45) for 31–48 months - 1.02 (0.83 to 1.25) for 49–72 months - 1.20 (0.99 to 1.46) for >72 months[a]
CML	
Titmarsh GJ, 2014	- 1.08 (0.82 to 1.43) for 13–30 months - 0.97 (0.70 to 1.35) for 31–48 months - 1.07 (0.79 to 1.44) for 49–72 months - 1.02 (0.74 to 1.41) for >72 months[a]
MM	
Brown LM, 2008	- 1.30 (0.58 to 2.90) for 2–4 years - 2.54 (1.47 to 4.40) for 5–9 years - 2.04 (1.30 to 3.21) for ≥10 years
Cuzick J, 1988	- 3.12 (1.18 to 8.24) for 1–3 years - 2.68 (0.66 to 10.80) for 3–5 years - 3.57 (1.38 to 9.25) for 5–10 years - 1.56 (0.93 to 2.61) for ≥10 years[b]
Gramenzi A, 1991	- 5.0 (1.6 to 15.9) for 1–10 years - 0.8 (0.3 to 2.1) for ≥10 years
McShane CM, *Int J Cancer*, 2014	- 1.44 (1.28 to 1.64) for 13–30 months - 1.48 (1.29 to 1.70) for 31–48 months - 1.42 (1.23 to 1.62) for 49–72 months - 1.19 (1.02 to 1.39) for >72 months
Nanni O, 1998	- 4.1 (1.1 to 15.2) for ≤10 years - 1.23 (0.4 to 4.4) for >10 years
Sørensen HT, 2004	- 4.8 (2.1 to 9.4) at 1 year - 1.7 (1.1 to 2.6) thereafter
HL	
Anderson LA, 2014	- 1.36 (0.95 to 1.94) for 13–30 months - 1.48 (1.00 to 2.19) for 31–48 months - 1.93 (1.38 to 2.70) for 49–72 months - 1.49 (1.00 to 2.22) for >72 months
Kristinsson SY, 2015	- Similar to overall results when stratifying by time periods
Sørensen HT, 2004	- None diagnosed at 1 year - 3.0 (1.1 to 6.6) thereafter
Tavani A, 2000	- 5.8 (2.7 to 12.1) for 1–10 years - 1.2 (0.4 to 3.1) for >10 years
Non-haematological overall	
Sørensen HT, 2004	- 1.7 (1.2 to 2.4) for 0–2 months - 1.5 (1.1 to 1.9) for 3–5 months - 0.9 (0.6 to 1.3) for 6–8 months - 0.8 (0.5 to 1.1) for 9–12 - 1.1 (1.0 to 1.2) for 1–4 years - 1.1 (1.0 to 1.2) for 5–9 years - 1.1 (1.0 to 1.3) for ≥10 years
Oesophagus	
Sørensen HT, 2004	- 1.3 (0.2 to 5.4) at 1 year - 1.5 (0.9 to 2.4) thereafter
Stomach	
Sørensen HT, 2004	- 1.1 (0.4 to 2.3) at 1 year - 1.3 (0.9 to 1.7) thereafter
Hepatobiliary	
Sørensen HT, 2004	- 1.5 (0.4 to 6.0) at 1 year - 1.3 (0.7 to 2.2) thereafter
Pancreas	
Sørensen HT, 2004	- 1.3 (0.5 to 2.7) at 1 year - 1.2 (0.8 to 1.6) thereafter
Colorectal	
Iglar K, 2013	- 0.92 (CI: N.R.) at 180 days - 1.03 (CI: N.R.) at 1 year - 1.02 (CI: N.R.) at 2 years - 1.02 (CI: N.R.) at 3 years - 1.00 (CI: N.R.) at 4 years

	- 1.01 (CI: N.R.) at 5 years
Mahale P, 2015	Colon alone: - 1.20 (1.04 to 1.38) for 13–35 months - 1.12 (0.98 to 1.29) for 36–59 months - 1.03 (0.91 to 1.16) for 60+ months
Sørensen HT, 2004	Colon alone: - 0.8 (0.4 to 1.4) at 1 year - 0.9 (0.7 to 1.1) thereafter Rectum alone: - 1.0 (0.4 to 2.0) at 1 year - 0.9 (0.7 to 1.2) thereafter
Kidney	
Sørensen HT, 2004	- 1.7 (0.6 to 3.8) at 1 year - 1.3 (0.9 to 1.8) thereafter
Bladder	
Sørensen HT, 2004	- 1.4 (0.8 to 2.5) at 1 year - 1.0 (0.7 to 1.2) thereafter
Prostate	
Iglar K, 2013	- 1.13 (CI: N.R.) at 180 days - 1.06 (CI: N.R.) at 1 year - 1.10 (CI: N.R.) at 2 years - 1.08 (CI: N.R.) at 3 years - 1.07 (CI: N.R.) at 4 years - 1.06 (CI: N.R.) at 5 years
Sørensen HT, 2004	- 1.4 (0.8 to 2.4) at 1 year - 1.2 (0.9 to 1.4) thereafter
Ovary	
Sørensen HT, 2004	- 2.3 (0.9 to 4.8) at 1 year - 1.1 (0.7 to 1.6) thereafter
Cervix uteri	
Sørensen HT, 2004	- 0.5 (0.01 to 2.5) at 1 year - 0.8 (0.4 to 1.5) thereafter
Uterus	
Sørensen HT, 2004	- 0.9 (0.2 to 2.6) at 1 year - 1.0 (0.6 to 1.4) thereafter
Breast	
Iglar K, 2013	- 1.09 (CI: N.R.) at 180 days - 1.06 (CI: N.R.) at 1 year - 1.03 (CI: N.R.) at 2 years - 1.03 (CI: N.R.) at 3 years - 1.04 (CI: N.R.) at 4 years - 1.02 (CI: N.R.) at 5 years
Sørensen HT, 2004	- 0.8 (0.4 to 1.4) at 1 year - 1.1 (0.9 to 1.3) thereafter
Oral cavity/pharynx	
Mahale P, 2015	- 1.46 (1.13 to 1.90) for 13–35 months - 1.18 (0.88 to 1.57) for 36-59 months - 1.06 (0.82 to 1.37) for 60+ months
Lung	
Iglar K, 2013	- 1.18 at (CI: N.R.) 180 days, 1.10 at 1 year - 1.08 at (CI: N.R.) 2 years, 1.06 at 3 years - 1.06 at (CI: N.R.) 4 years - 1.05 at (CI: N.R.) 5 years
Mahale P, 2015	- 1.21 (1.07, 1.38) for 13–35 months - 1.16 (1.02, 1.32) for 36–59 months - 1.01 (0.90, 1.13) for 60+ months
Sørensen HT, 2004	- 1.4 (0.9 to 2.2) at 1 year - 1.2 (1.0 to 1.4) thereafter
Eye, brain, other CNS	
Sørensen HT, 2004	- None diagnosed at 1 year - 1.6 (1.1 to 2.3) thereafter
Sarcoma	
Franceschi S, 1992	- Highest estimate for herpes zoster within 3 years before diagnosis (estimates N.R.)
Sørensen HT, 2004	- 2.7 (0.6 to 7.8) at 1 year - 1.1 (0.5 to 2.1) thereafter
Melanoma	

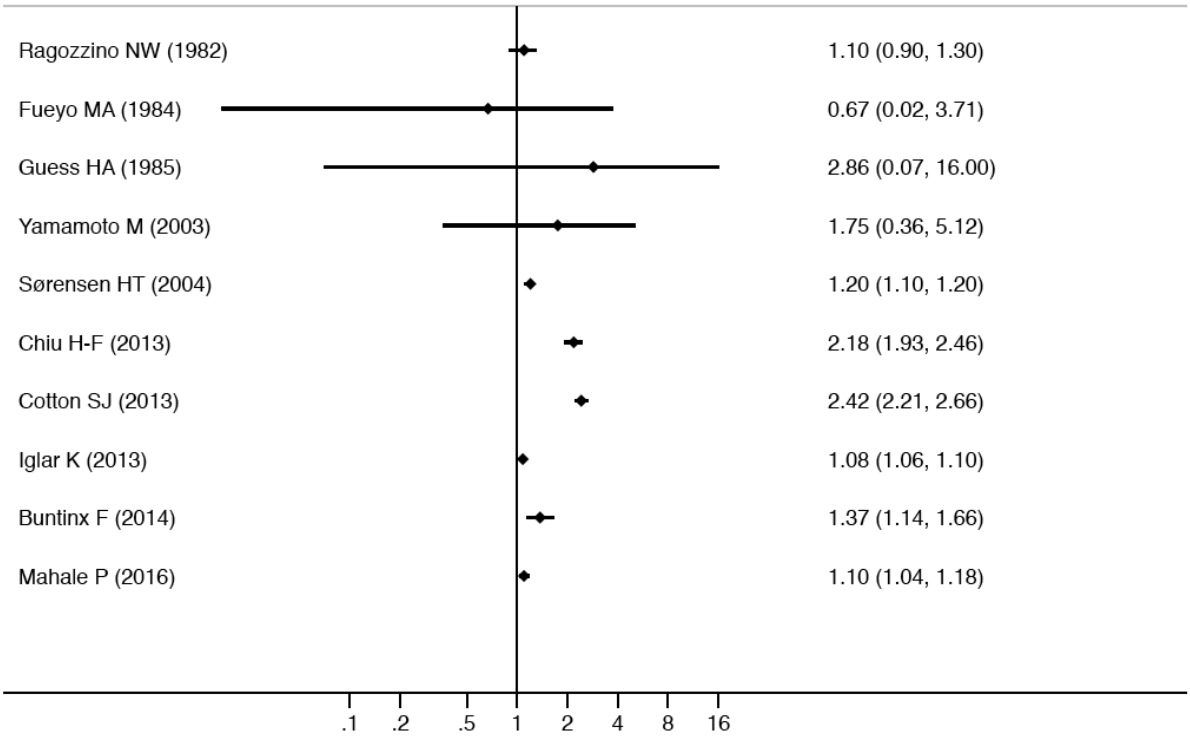
Sørensen HT, 2004	- 0.5 (0.01 to 2.5) at 1 year - 0.8 (0.5 to 1.3) thereafter
NMSC excluding basal cell and squamous cell carcinoma	
Mahale P, 2015	- 1.47 (0.96 to 2.23) for 13–35 months - 1.78 (1.23 to 2.57) for 36–59 months - 1.25 (0.88 to 1.77) for 60+ months
Any NMSC	
Sørensen HT, 2004	- 1.1 (0.7 to 1.7) at 1 year - 1.1 (1.0 to 1.3) thereafter
'Other'	
Iglar K, 2013	- 1.27 (CI: N.R.) at 180 days - 1.17 (CI: N.R.) at 1 year - 1.13 (CI: N.R.) at 2 years - 1.11 (CI: N.R.) at 3 years - 1.11 (CI: N.R.) at 4 years - 1.11 (CI: N.R.) at 5 years

Abbreviations: AML = acute myeloid leukemia; CI=confidence interval; CLL=chronic lymphocytic leukemia; CML=chronic myeloid leukemia; HL=Hodgkin's lymphoma; LPL=lymphoplasmacytic lymphoma; MM=multiple myeloma; NHL= Non-Hodgkin's lymphoma; NMSC=non-melanoma skin cancer; N.R.=not reported; WM=Waldenström's macroglobulinemia

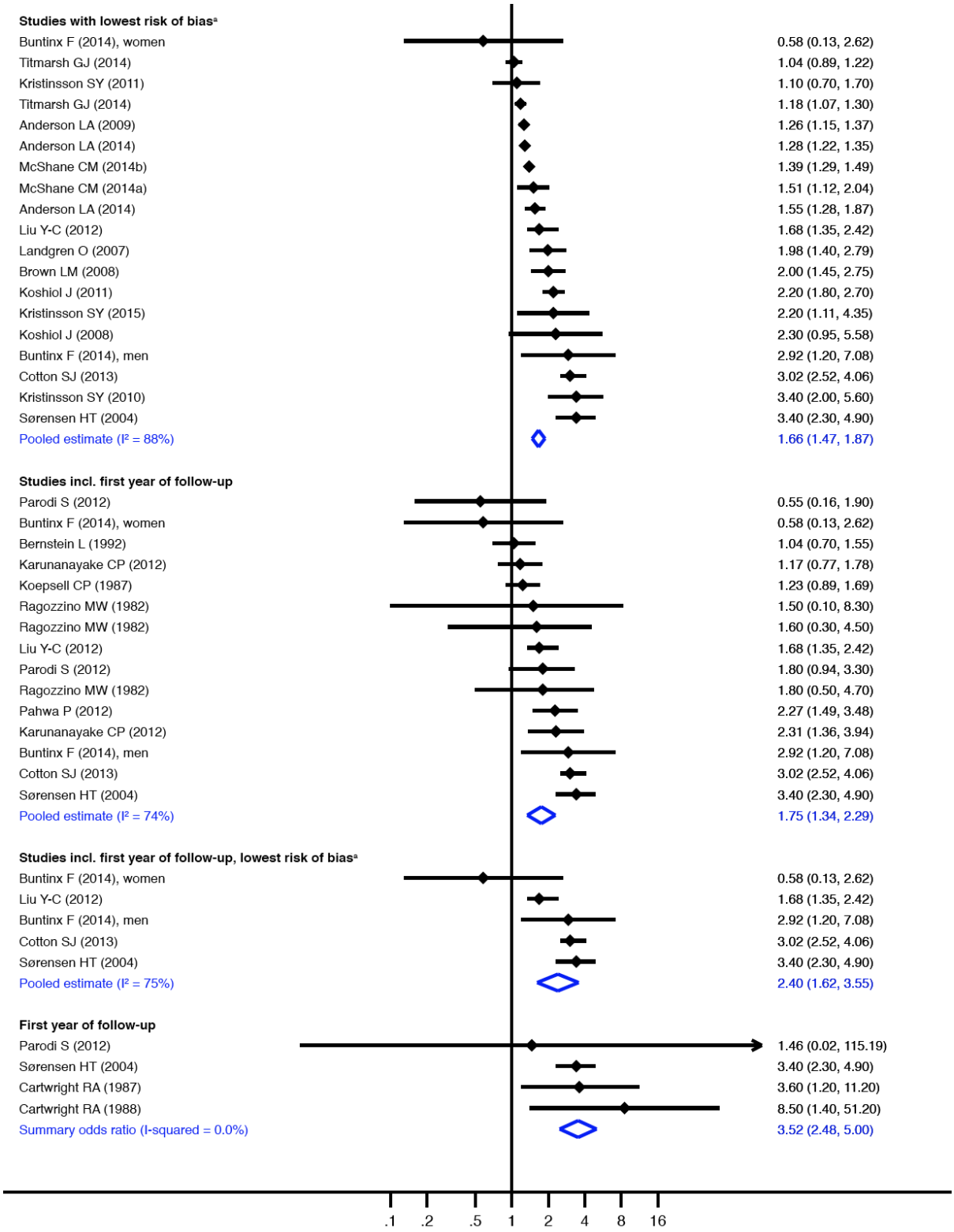
[a]Provided by author

[b]Reported time periods are not exclusive

Web Figure 1. Relative risk estimates (95% confidence intervals) for the association between herpes zoster and subsequent diagnosis of cancer, ordered by publication year

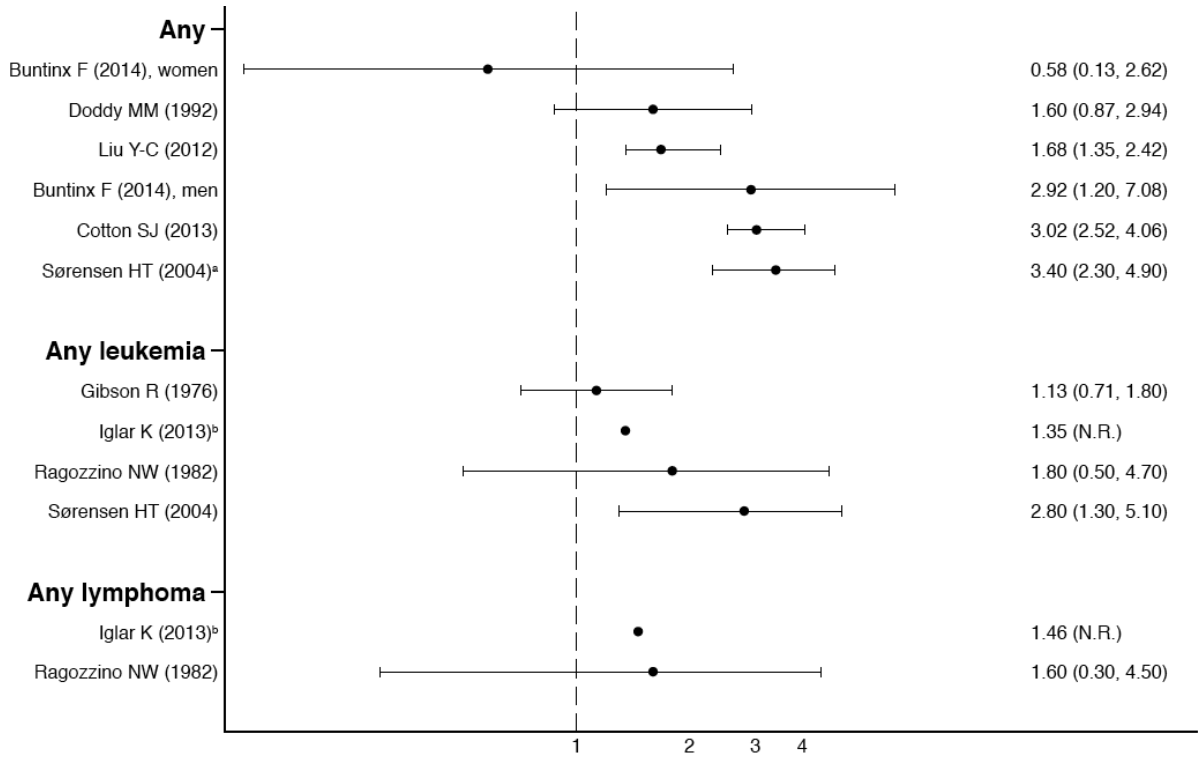


Web Figure 2. Relative risk estimates (95% confidence intervals) for the association between herpes zoster and subsequent diagnosis of any hematological cancer, ordered according to the magnitude of the effect estimate



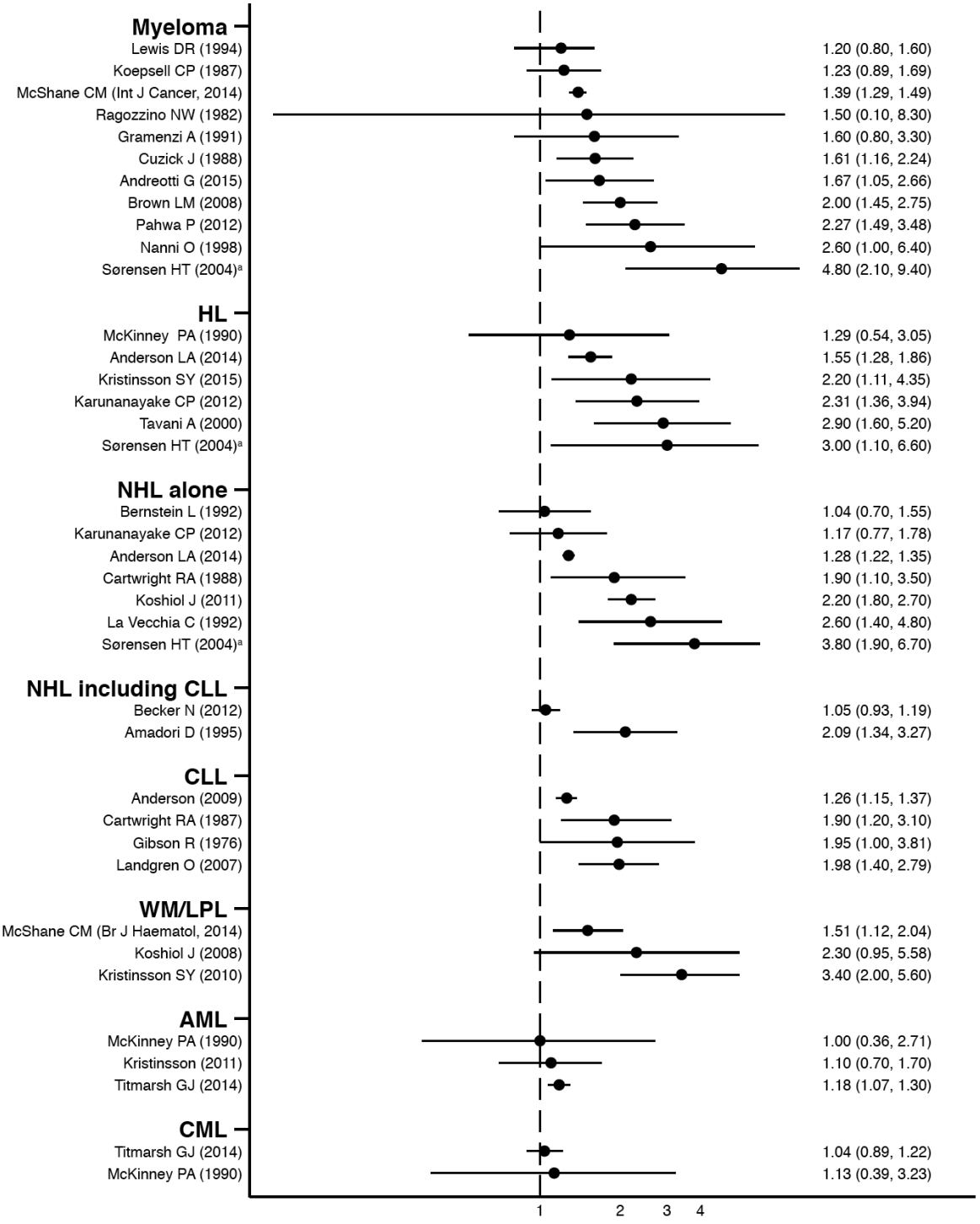
*Excludes studies with high risk of bias stemming from use of self- or proxy-reported data on herpes zoster, use of hospital controls in case-control studies, potential selection bias due to non-participation, or lack of adjustment for age and/or sex.

Web Figure 3. Relative risk estimates (95% confidence intervals) for the association between herpes zoster and subsequent diagnosis of hematological cancer, ordered according to the magnitude of the effect estimate



Abbreviations: N.R.=not reported
[a]Represents the relative risk at 1 year, as overall estimate was not reported.
[b]Was not included in the meta-analysis, as only effect estimates were reported.

Web Figure 4. Relative risk estimates (95% confidence intervals) for the association between herpes zoster and subsequent diagnosis of individual types of hematological cancers, ordered according to the magnitude of the effect estimate

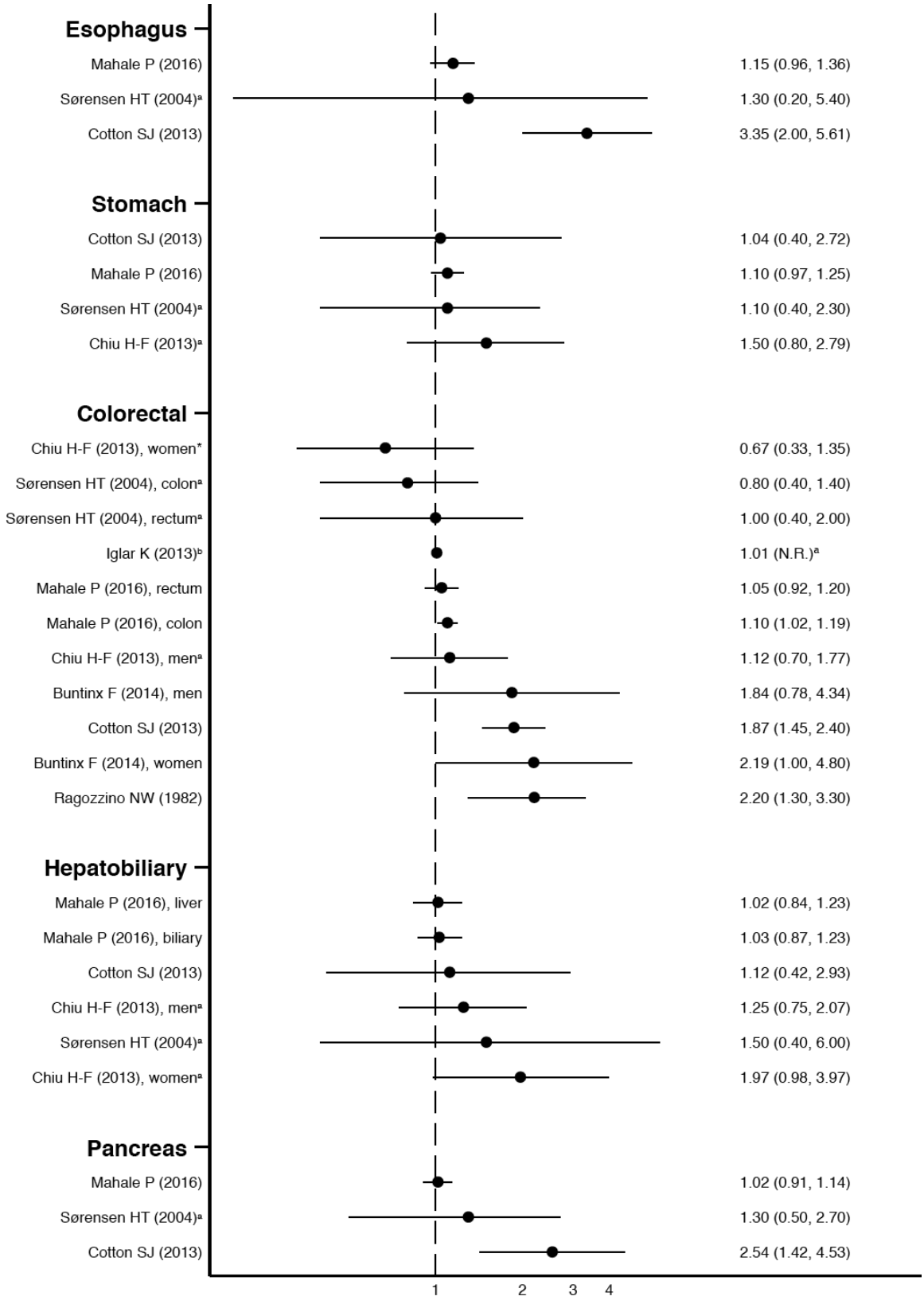


Abbreviations: AML = acute myeloid leukemia; CLL=chronic lymphocytic leukemia; CML=chronic myeloid leukemia; HL=Hodgkin's lymphoma; LPL=lymphoplasmacytic lymphoma; MM=multiple myeloma; NHL= Non-Hodgkin's lymphoma; WM=Waldenström's macroglobulinemia

[a]Represents the relative risk at 1 year, as overall estimate was not reported.

Note: Only the study by McKinney *et al.* (1990) reported data on acute lymphocytic leukemia, showing an odds ratio of 9.50 (0.96, 93.79).

Web Figure 5. Relative risk estimates (95% confidence intervals) for the association between herpes zoster and subsequent diagnosis of gastrointestinal cancers, ordered according to the magnitude of the effect estimate

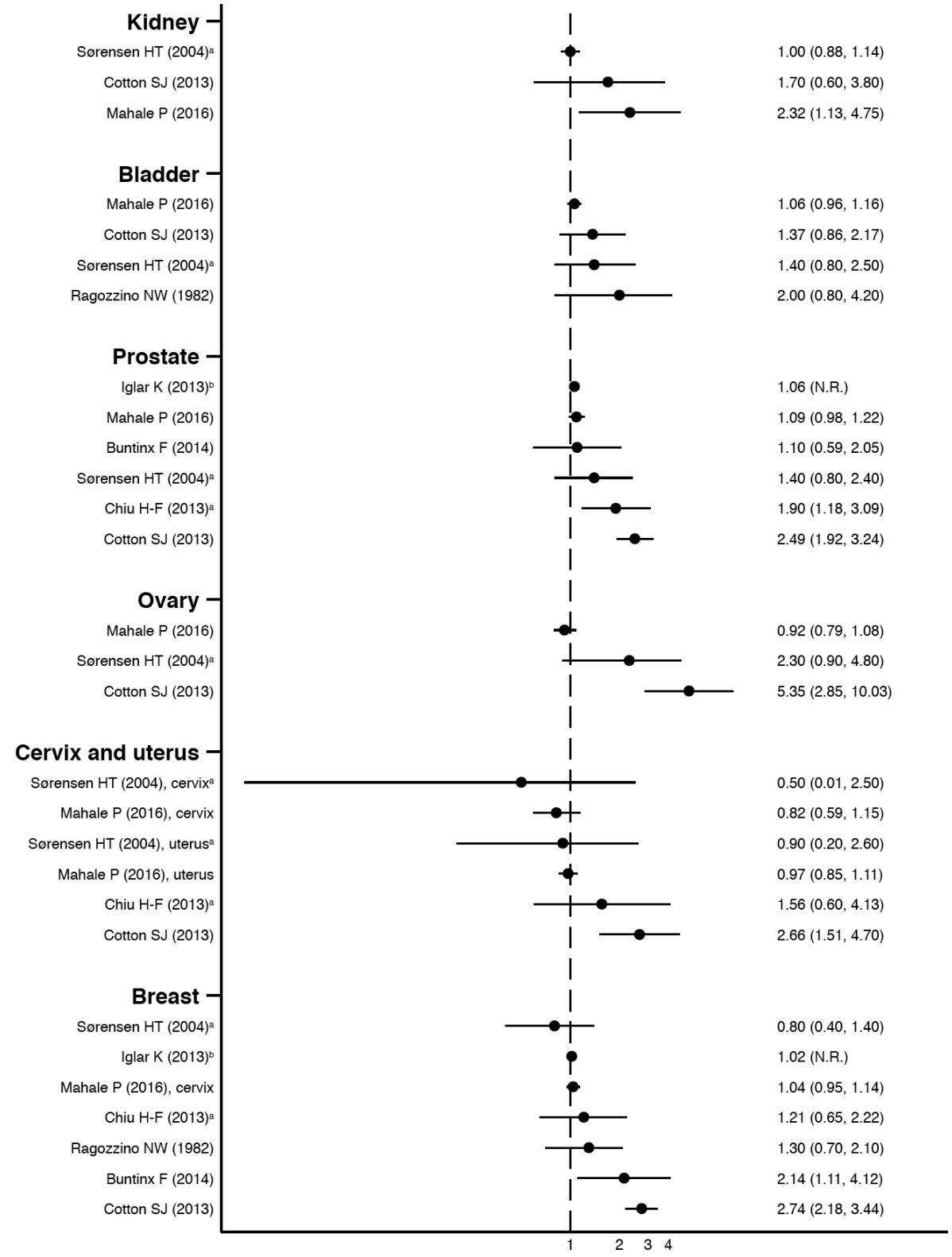


Abbreviation: N.R.=Not reported confidence interval

[a]Represents the relative risk at 1 year, as overall estimate was not reported.

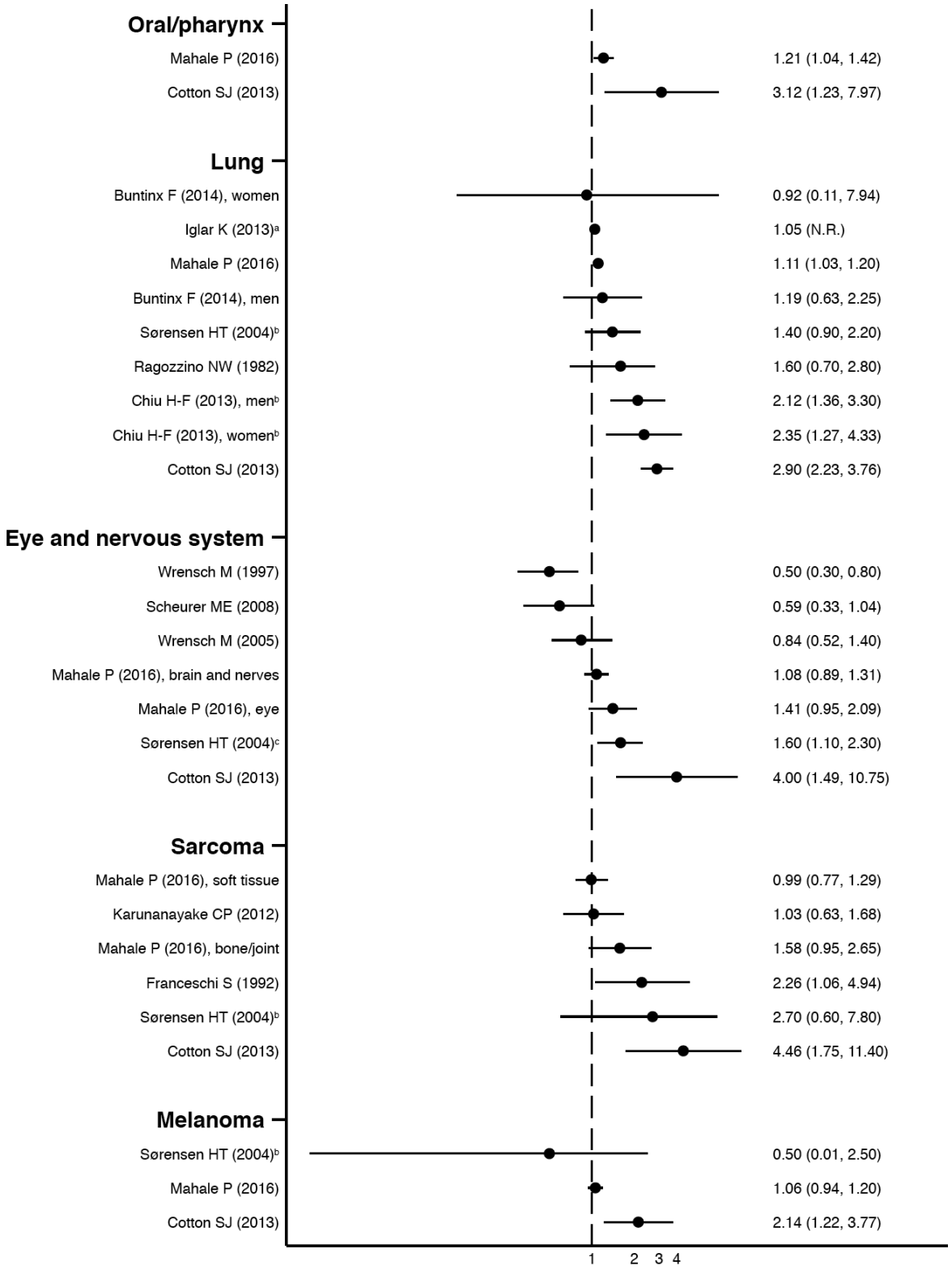
[b]Was not included in the meta-analysis, as only effect estimates were reported.

Web Figure 6. Relative risk estimates (95% confidence intervals) for the association between herpes zoster and subsequent diagnosis of genitourinary and breast cancers, ordered according to the magnitude of the effect estimate



Abbreviation: N.R.=Not reported confidence interval
[a]Represents the relative risk at 1 year, as overall estimate was not reported.
[b]Was not included in the meta-analysis, as only effect estimates were reported.

Web Figure 7. Relative risk estimates (95% confidence intervals) for the association between herpes zoster and subsequent diagnosis of other cancers, ordered according to the magnitude of the effect estimate



Abbreviation: N.R.=Not reported confidence interval

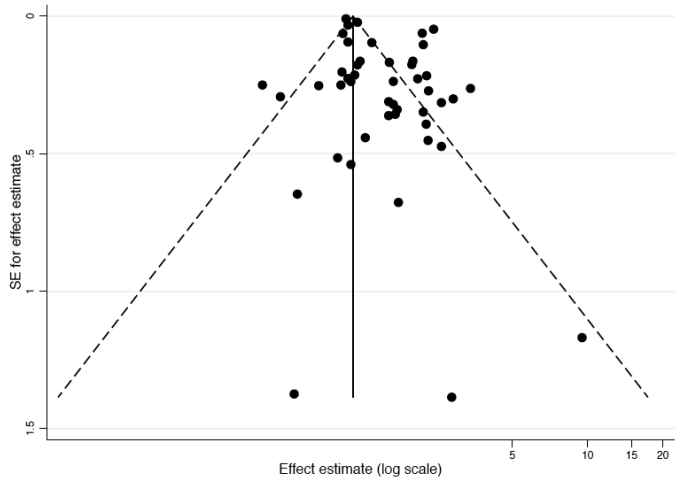
[a]Was not included in the meta-analysis, as only effect estimates were reported.

[b]Represents the relative risk at 1 year, as overall estimate was not reported.

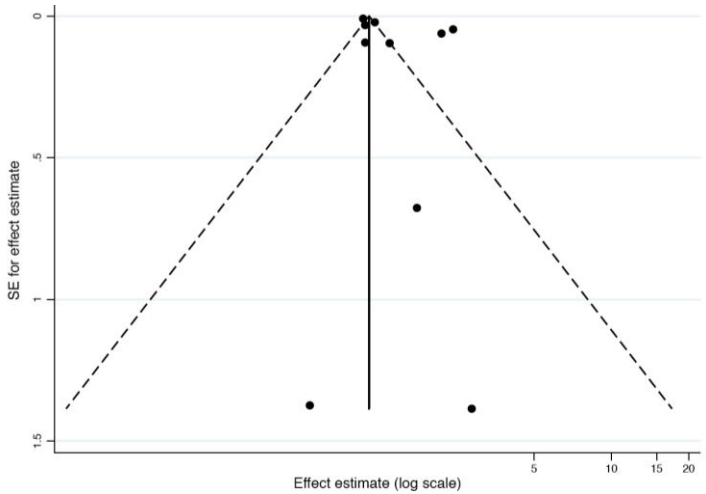
[c]Represents the relative risk after 1 year, as an overall estimate was not reported and no events were observed in the first year.

Web Figure 8. Funnel plots of the log odds ratio plotted against the standard error of the log odds ratio for included studies (dotted lines represent pseudo 95% confidence intervals)

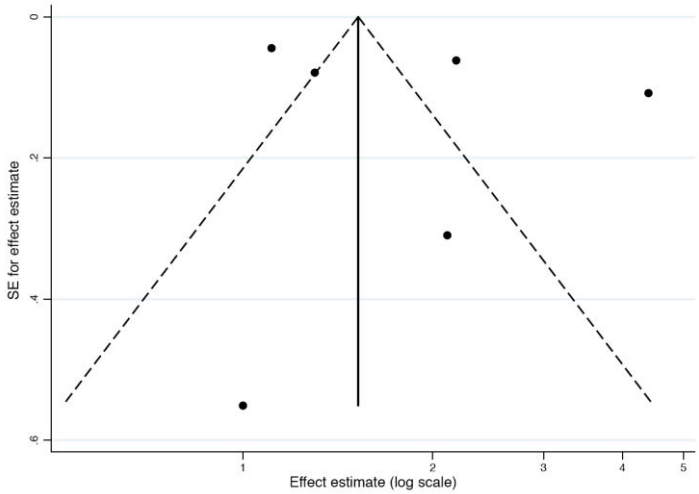
A) All included studies combined



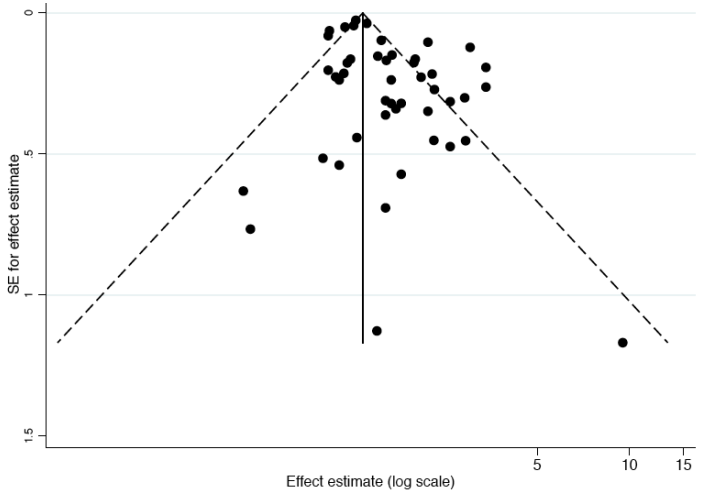
B) Studies on overall cancer



C) Studies on overall cancer within 1 year after herpes zoster



D) Studies on hematological cancer



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Declaration of co-authorship

Full name of the PhD student: Sigrun Alba Johannesdottir Schmidt

This declaration concerns the following article/manuscript:

Title:	Prevaccination epidemiology of herpes zoster in Denmark: quantification of occurrence and risk factors
Authors:	Sigrun A J Schmidt, Mogens Vestergaard, Lisbeth M Baggesen, Lars Pedersen, Henrik C Schønheyder, Henrik T Sørensen

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☒ In preparation ☐

If published, state full reference:

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

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The PhD student has contributed to the elements of this article/manuscript as follows:

A. No or little contribution
B. Has contributed (10-30 %)
C. Has contributed considerably (40-60 %)
D. Has done most of the work (70-90 %)
E. Has essentially done all the work

Element	Extent (A-E)
1. Formulation/identification of the scientific problem	D
2. Planning of the experiments and methodology design and development	D
3. Involvement in the experimental work/clinical studies/data collection	D
4. Interpretation of the results	D
5. Writing of the first draft of the manuscript	E
6. Finalization of the manuscript and submission	D

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This declaration concerns the following article/manuscript:

Title:	Partner Bereavement and Risk of Herpes Zoster: Results from Two Population-Based Case-Control Studies in Denmark and the United Kingdom.
Authors:	Sigrun A J Schmidt, Mogens Vestergaard, Henrik S Pedersen, Henrik C Schønheyder, Sara L Thomas, Liam Smeeth, Kathryn E Mansfield, Henrik T Sorensen, Harriet J Forbes, and Sinéad M Langan

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preparation ☐

If published, state full reference: Schmidt SA, Vestergaard M, Pedersen HS, Schønheyder HC, Thomas SL, Smeeth L, Mansfield KE, Sørensen HT, Forbes HJ, Langan SM. Partner Bereavement and Risk of Herpes Zoster: Results from Two Population-Based Case-Control Studies in Denmark and the United Kingdom. Clin Infect Dis. 2016. DOI: 10.1093/cid/ciw840 [Online ahead of print]

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5. Writing of the first draft of the manuscript	E
6. Finalization of the manuscript and submission	D

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This declaration concerns the following article/manuscript:

Title:	Mood disorders and risk of herpes zoster in two population-based case-control studies in Denmark and the United Kingdom
Authors:	Sigrun A J Schmidt, Sinéad M Langan, Henrik S Pedersen, Henrik C Schønheyder, Sara L Thomas, Liam Smeeth, Kathryn E Mansfield, Henrik T Sorensen, Harriet J Forbes, and Mogens Vestergaard

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☒ In preparation ☐

If published, state full reference:

If accepted or submitted, state journal: Clin Infect Dis

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Title:	Herpes zoster as a marker of occult cancer: A systematic review and meta-analysis.
Authors:	Sigrun A J Schmidt, Anil Mor, Henrik C Schønheyder, Henrik T Sørensen, Olaf M Dekkers, and Deirdre Cronin-Fenton

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preparation ☐

If published, state full reference: Schmidt SA, Mor A, Schønheyder HC, Sørensen HT, Dekkers OM, Cronin-Fenton D. Herpes zoster as a marker of occult cancer: A systematic review and meta-analysis. J Infect. 2016. doi: 10.1016/j.jinf.2016.11.005. [Online ahead of print]

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Element	Extent (A-E)
1. Formulation/identification of the scientific problem	E
2. Planning of the experiments and methodology design and development	D
3. Involvement in the experimental work/clinical studies/data collection	D
4. Interpretation of the results	D
5. Writing of the first draft of the manuscript	E
6. Finalization of the manuscript and submission	D

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