BJD
British Journal of Dermatology

Perceived psychological stress and risk of herpes zoster: a nationwide population-based cohort study

S.A.J. Schmidt [1,2] H.T. Sørensen,[1] S.M. Langan[3] and M. Vestergaard[4]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark
[3]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK
[4]Research Unit for General Practice, Aarhus University, Aarhus, Denmark

Correspondence
Sigrun A.J. Schmidt.
Email: saj@clin.au.dk

Accepted for publication
26 January 2021

Funding sources
This work was supported by the Edel and Wilhelm Daubenmerkls Charitable Foundation (grant number 100060), the Lundbeck Foundation (grant number R248-2017-521) and the Program for Clinical Research Infrastructure established by the Lundbeck Foundation and the Novo Nordisk Foundation. The funder had no role in the study design, data collection, data analysis, manuscript preparation and/or publication decisions.

Conflicts of interest
S.A.J.S. reports receipt of grants from the Edel and Wilhelm Daubenmerkls Charitable Foundation during the study period. H.T.S. reports receipt of grants from the Lundbeck Foundation (R248-2017-521) during the study period, and the Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies are related to the present study. S.M.L. reports receipt of grants from the Wellcome Trust and the National Institute for Health Research during the study period.

DOI 10.1111/bjd.19832

Summary

Background Psychological stress may reduce cellular immunity, but its role in triggering latent infections, including herpes zoster (HZ), is controversial.
Objectives To examine the association between perceived psychological stress and risk of HZ.
Methods In a linked registry-based cohort study, we followed 77 310 persons aged 40 years or older who participated in the 2010 Danish National Health Survey from 1 May 2010 until HZ diagnosis, death, emigration or 1 July 2014, whichever occurred first. We computed hazard ratios (HRs) of HZ associated with Cohen's Perceived Stress Scale (PSS) score (range 0–40) using Cox regression with age as the timescale, adjusted for sex, immunosuppressive and selected chronic conditions, immunosuppressive drugs, and sociodemographic, lifestyle and anthropometric factors. The PSS measures chronic stress perceived by an individual in response to various demands of daily life. We modelled the PSS score using quintiles and a restricted cubic spline function.
Results The unadjusted rate of HZ varied from 5·53 to 7·20 per 1000 person-years from the lowest to the highest PSS score quintile. Compared with the lowest PSS score quintile, the adjusted HR for HZ was 1·00 [95% confidence interval (CI) 0·86–1·16], 1·08 (95% CI 0·92–1·26), 1·05 (95% CI 0·90–1·23) and 1·14 (95% CI 0·97–1·34) for the second to the fifth quintile, respectively. In cubic spline analyses, PSS scores < 20 were not associated with increased HR of HZ, but thereafter the HR increased linearly from 1·10 (95% CI 0·85–1·41) to 2·22 (95% CI 1·32–3·75).
Conclusions Our study indicated that high levels of psychological stress are associated with increased risk of HZ.

What is already known about this topic?

- Psychological stress may reduce cellular immunity, but its role in triggering latent infections, such as herpes zoster (HZ), is controversial.
- Previous epidemiological studies have mainly focused on the effects of negative life events (e.g. bereavement) on HZ risk, and dose–response analyses are lacking.
- It is possible that the allostatic load (the cumulative 'wear and tear' on the body associated with stress) depends on the type of stress and coping mechanisms.

What does this study add?

- In this large population-based cohort study, we found that persons reporting the highest levels of perceived psychological stress in daily life had an increased risk of HZ.
- Perceived psychological stress may be a modifiable risk factor for HZ.

- Our study adds HZ to the growing list of potential negative health consequences of psychological stress and underscores the importance of supporting mental wellbeing and resilience in the general population.

Acute and chronic psychological stress are associated with decreased counts and activity of cytotoxic lymphocytes, mediated mainly through hyperarousal of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis.[1,2] Depression of cellular immune function could possibly increase the risk of reactivation of latent infections,[1,2] such as the varicella zoster virus (VZV), which causes herpes zoster (HZ).[3]

Previous studies on stress and the risk of HZ have reported conflicting results. Two large registry-based studies (a case–control study and a self-controlled case series) found no increase in HZ risk following partner bereavement, which is a severe stressor.[4,5] In contrast, five small studies observed an increase in the relative risk of HZ of 40% or more among persons reporting a wide range of negative life events compared with those not reporting such events,[6–10] but possible selection and recall bias,[6–10] lack of interviewer blinding[7–10] and small sample sizes raise doubts regarding these findings.[6–10] Furthermore, the use of negative life events as objective indicators of stress may not provide a valid and complete picture of the association between stress and HZ, as psychological stress depends on the type and duration of the stressor and on personal coping mechanisms.[2] Only one small cohort study from Japan examined the risk of HZ associated with perceived stress in daily life. This study found that men with very high stress levels had an approximately twofold higher risk of HZ compared with those reporting low stress levels.[11] However, stress was crudely measured by asking participants to rate their overall level of daily stress, dose–response analyses were not provided and the sample size was limited (< 10 outcomes among men and women reporting a very high stress level).

We addressed the limitations of previous studies in a large population-based cohort study on the association between psychological stress and the risk of HZ in persons aged 40 years or older. We based the study on a large nationwide Danish survey, which included a validated instrument to measure perceived stress in various aspects of daily life and performed dose–response analyses to avoid disregarding any potential threshold effects.

Materials and methods

Study population

The cohort included participants in the Danish National Health Survey – a nationwide cross-sectional survey conducted in 2010 among Danish inhabitants aged ≥ 16 years on 1 January 2010.[12] The survey included six mutually exclusive random samples, i.e. five stratified samples from each of the five Danish Regions and one national sample.[12] Sampling was performed through the Civil Registration System, which maintains a database of unique personal identifiers issued to all Danish residents.[13] In total, 298 850 persons were invited to take part in the survey and 60% accepted.[12] Calibrated nonresponse weights were computed based on selected characteristics identified through linkage to other data sources.[12,14]

A standard questionnaire with 52 questions addressing sociodemographic characteristics, health-related quality of life, health behaviour, morbidity, consequences of illness and social relations was used in all six survey samples, but the jurisdiction responsible for each sample could include additional questions or exclude questions.

For the current study, we had access to selected survey variables for the population aged ≥ 25 years on 1 January 2010. We defined 1 May 2010 (the date when questionnaire collection was completed) as the baseline for all participants. We excluded responders who completed the questionnaire but died or emigrated before 1 May 2010. We also excluded participants from the South Denmark Region sample, as questions on perceived stress were not included in their questionnaire.

We linked the survey data to records of hospital diagnoses and treatment in the Danish National Patient Registry[15] and the Danish Central Psychiatric Research Registry,[16] to prescriptions recorded in the Danish National Prescription Registry,[17] to demographic and vital status data in the Civil Registration System,[13] and to education level as recorded in the Population Education Registry.[18] Additional information on the survey and the linked data sources is provided in Appendix S1 (see Supporting Information).

Exposure

We measured psychological stress using the Danish 10-item version of Cohen's Perceived Stress Scale (PSS),[19,20] which includes questions about whether a person perceives various situations in daily life (e.g. unexpected events, irritations of daily life, personal problems) to have been unpredictable, uncontrollable or overwhelming during the past month. Each question is scored on a scale of 0–4; four positively worded items are inversely scored. We included the total PSS score (range 0–40) as a categorical variable based on quintiles (0–6, 7–10, 11–13, 14–17 and ≥ 18 points) and as a continuous variable. A higher PSS score indicates a higher degree of perceived stress and scores in the highest quintile are generally considered abnormal.[21] Detailed code lists for the PSS score and other study variables, including the questions used in the survey, are available in Table S1 (see Supporting Information).

Outcome

We defined HZ using a validated algorithm based on hospital diagnoses and antiviral prescriptions, as defined in previous studies.[4,22,23] We identified all first-time inpatient, outpatient (ambulatory) clinic, and emergency room primary and secondary HZ discharge diagnoses in the Danish National Patient Registry. We used the Danish National Prescription Registry to identify first-time antiviral prescriptions likely to represent treatment for HZ (packages with 35 pills of 800 mg aciclovir or a 500-mg tablet dose of valaciclovir or famciclovir) as a surrogate for HZ treated outside the hospital setting (which is not recorded in any Danish registry). We limited the study to persons who were aged 40 years or older at baseline and who had no previous diagnosis of HZ or postherpetic neuralgia or prescription for aciclovir, valaciclovir or famciclovir at any dose. We used the date of hospitalization or prescription, whichever occurred first, as the diagnosis date. The HZ vaccine was not available in Denmark during the study period.

Covariables

We used existing evidence on HZ risk factors[24] to construct a directed acyclic graph illustrating the conceptual framework for the association between perceived stress and HZ (Figure S1; see Supporting Information). We then identified relevant potential confounders measured before or at baseline using self-reported and administrative data from our data sources (detailed definitions available in Table S1; see Supporting Information). Besides age and sex, risk factors included the following immune-mediated and immunosuppressive chronic conditions/states: rheumatoid arthritis, systemic/subacute lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, diabetes mellitus, chronic kidney disease, severe immunosuppression (HIV infection, haematopoietic stem cell transplantation, other cellular immune deficiency, leukaemia, lymphoma, myeloma, use of oral glucocorticoids or other immunosuppressant drugs), hospital-diagnosed mood disorder (depression, anxiety, stress disorder or adjustment disorder) and use of inhaled glucocorticoids.[22,24] We also included the following lifestyle and anthropometric factors: smoking status (never, former or current), weekly alcohol consumption (low-risk, intermediate-risk or high-risk use), body mass index (underweight, normal weight, overweight or obese) and physical activity (sedentary, light or moderate/vigorous). We identified education level [short (< 10 years), intermediate (10–15 years) or high (> 15 years)] as a measure of socioeconomic status, which may affect health-seeking behaviour (and thus the chance of being diagnosed and treated for HZ),[25] lifestyle and perception of stress. We included country of origin (Danish, other Western or non-Western) as a proxy for ethnicity, which is associated with HZ (e.g. South Asian and black populations are at lower risk)[25] and is potentially linked to lifestyle through socioeconomic or other (e.g. genetic) factors.

Statistical analysis

We followed persons from baseline until HZ diagnosis, death, emigration or 1 July 2014, whichever came first. We characterized the study population using covariables, overall and using PSS score quintiles. We computed the number of events, accumulated person-time and incidence rate of HZ for each quintile.

We used the Cox proportional hazard regression model[26] stratified by 5-year birth cohorts to compute crude HRs for HZ for each PSS score quintile using the lowest category as reference. In the analysis of PSS score as a continuous variable, we entered the total score into the model as a restricted cubic spline with five knots placed at equally spaced centiles.[27] In restricted cubic spline regression, a cubic polynomial (i.e. a polynomial of degree 3) is fitted to the segment of data between two 'knots' placed at different values of the continuous predictor variable.[27] The researcher determines the number and position of knots. The model is restricted in the sense that the splines are constrained to be linear before the first knot and after the last knot. At each knot, the curves for the adjacent segments are connected and smoothened without jumps. This flexible method thus allows for smooth nonlinear presentation of the relation between a continuous variable and an outcome without losing potentially important information through categorization or assumptions of linearity. We used age as the underlying timescale in the Cox model, because age is strongly associated with rate of HZ and because it did not require us to specify a specific linear or nonlinear association between age and HZ. We explored the effect of adjusting for covariables by fitting sequential multivariable models as follows: model 1 adjusted for sex, model 2 additionally included immune-related diseases and immunosuppressive drugs, model 3 additionally included country of origin and education level, and model 4 additionally adjusted for smoking status, weekly alcohol consumption, BMI and physical activity. We based the restricted cubic splines regression on model 4. We examined for collinearity among variables from the full model using variation inflation factors (VIFs). We considered individual VIF values of ≥ 10 or a mean value substantially over 1·0 to be cause for concern. We performed prespecified analyses in subgroups of age (< 50, 50–59, 60–69, 70–79 and ≥ 80 years) and sex to examine effect measure modification. We incorporated calibrated weights in all analyses to account statistically for survey design and differential nonresponse.[14] We assessed the proportional hazards assumption by visual inspection of log–log plots and found it to be valid.

All analyses were performed using Stata software version 15 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency (record number 2013-41-1719). Approval by an ethics review board and informed consent were not required. The study protocol is available from the corresponding author upon request.

Missing data

There were missing data for self-reported variables, including PSS score. We considered that the 'missing at random' assumption for multiple imputation was inappropriate, as response could depend on the true value (e.g. missing data on alcohol consumption among heavy drinkers). In an attempt to frame plausible assumptions for the correct missingness mechanism,[28] we examined the distribution of missing data, summarized data by missingness pattern, and computed odds ratios using logistic regression with an indicator for missingness as the dependent variable and variables from the fully adjusted model as the independent variable.[28] We also compared the HRs of HZ for covariables based solely on registry data among survey nonresponders and among those with complete data for study variables. We found that 84% had complete data for all variables, and frequency of missing data for individual variables varied between 2·0% for education level to 6·9% for PSS score (Table S2; see Supporting Information). Both descriptive analyses (Table S3; see Supporting Information) and multivariable logistic regression (Table S4; see Supporting Information) showed that missingness was not associated with HZ, but with several confounders, including older age, female sex, several chronic diseases, non-Western country of origin, and for certain individual variables with missing data, shorter education, low-risk alcohol consumption, being underweight, a more sedentary lifestyle and a higher PSS score. These results suggest that missingness is conditionally independent of the outcome, and thus a complete case regression analysis provides asymptotically unbiased estimates of the exposure association.[28] Therefore, we analysed data using this approach. The HRs for HZ associated with covariables were similar for nonresponders and the final study population with complete data (Figure S2, see Supporting Information).

Results

The study flowchart is presented in Figure 1. Of 298 850 persons invited to participate in the survey, 202 137 were alive and aged ≥ 40 years at baseline, and of these 128 029 (63%) responded. We included 77 310 persons after excluding responders who had a history of HZ or antiviral treatment, who had missing data or were living in study regions that did not measure perceived stress in the questionnaire.

Mean age was 58 years (SE 0·049) and sex was equally distributed (Table 1). Women, persons with certain long-term conditions, shorter education and non-Western country of origin, and persons who were current smokers, were obese or had a sedentary lifestyle had higher PSS scores (Table S5; see Supporting Information).

We followed the entire cohort for 274 645 person-years (mean follow-up time 4·03 years, SE 0·0025) and observed 1686 events of incident HZ. The unadjusted rate of HZ varied from 5·53 to 7·20 per 1000 person-years in the lowest to the highest PSS score quintile (Table 2). We observed an increased hazard of HZ for the highest PSS score quintile [HR 1·21, 95% confidence interval (CI) 1·03–1·41], which decreased slightly upon adjustment (fully adjusted HR 1·14, 95% CI 0·97–1·34). When analysing PSS score as a cubic spline, we found that the fully adjusted HR was neutral until reaching a PSS score of 20, after which the HR increased linearly from 1·10 (95% CI 0·85–1·41) for persons with a PSS score of 20 to 2·22 (95% CI 1·32–3·75) for those with a PSS score of 40 (Figure 2). We did not observe meaningful differences between HRs in subgroups defined by age or sex (Table S6; see Supporting Information).

Discussion

In this population-based cohort study, we found that persons reporting high levels of perceived stress (i.e. a PSS score ≥ 18) had a 14% elevated relative risk of HZ after adjusting for age, sex, immune-related diseases, use of immunosuppressive drugs and lifestyle factors. We found some evidence of a threshold effect at a PSS score of about 20, after which the HR increased linearly. Thus, the risk of HZ was virtually the same for the 80% of the study population with lower PSS scores.

Four small case–control studies (n = 44–389 cases; n = 44–511 controls) and one cohort study (n = 4162) reported more than 40% increased relative risk of HZ within 2 months to 1–4 years after various negative life events, including health-related, financial, occupational and other types of stressful events identified by, for example, the Geriatric Scale of Recent Life Events or the Paykel list.[6–10] The validity of these studies is threatened by possible selection bias owing to missing data, volunteer bias or use of selected hospital controls (Berksonian bias), misclassification of exposures owing to differential recall and/or lack of interviewer blinding, and confounding as most studies lacked detail on important HZ risk factors or were too small to perform multiple adjustment. In contrast, a self-controlled case series (n = 39 811) based on US claims data found no increase in risk of HZ within 90 days after a death or catastrophic health event occurring in a partner (incidence rate ratio 0·76, 95% CI 0·54–1·06).[5] Similarly, we observed no increased risk of HZ following partner bereavement (odds ratio 1·03, 95% CI 0·98–1·08) in a previous study combining data from the UK and Denmark (n = 340 878 cases; n = 1 339 562 controls).[4] Thus, current methodologically sound evidence does not support an association between major negative life events and HZ.

Data on the association between perceived stress and HZ are very limited. One Japanese cohort study followed 12 352 persons aged 50 years or older for 3 years and found that men (HR 2·22, 95% CI 1·05–4·66), but not women (HR 0·78, 95% CI 0·37–1·65), had higher risk of HZ if they reported very high stress levels compared with those who reported low stress levels.[11] Stress was assessed using the question 'What is the level of stress in your daily life?', which was rated as low, medium, high or extremely high. A US case–control study including 389 cases of HZ diagnosed at clinics and hospitals in the Rochester Epidemiology Project in Olmsted County (MN, USA) and 511 matched hospital controls seeking care at

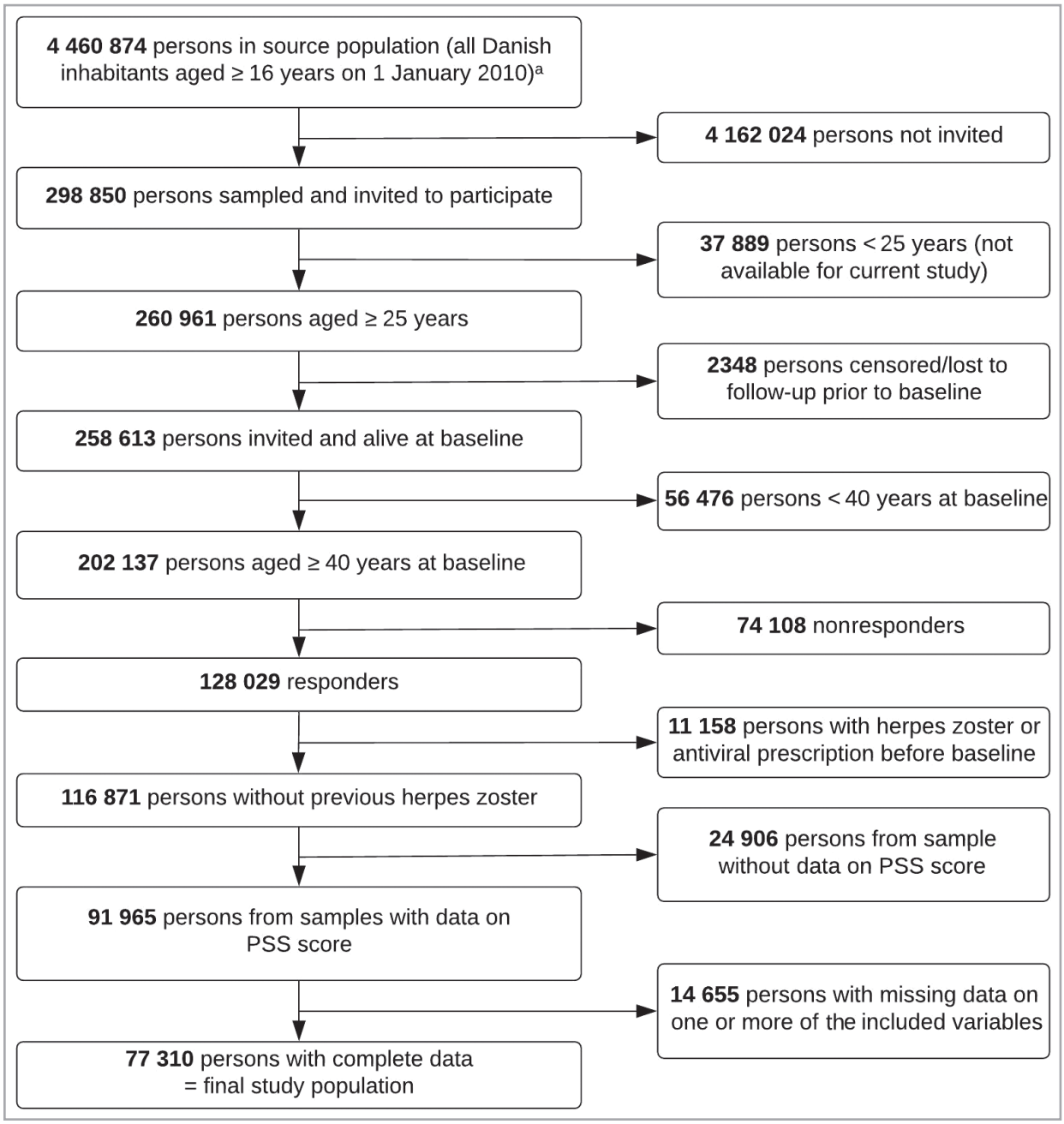

Figure 1 Study flowchart for selection of participants with PSS scores for study on association between stress and herpes zoster, Danish National Health Survey 2010–2014PSS, Perceived Stress Scale. [a]Number estimated using StatBank Denmark (statistikbanken.dk).

the same clinics for other unrelated conditions (intended matching at least 1 : 1) found a median stress score of 7 in both groups, using a scale from 0 (none) to 10 (worst imaginable).[9] The use of crude nonvalidated stress scales and lack of detailed dose–response analyses impede interpretation of the results from these two studies. Furthermore, recall bias and reverse causality cannot be excluded in the US study, where stress was assessed at or shortly after HZ diagnosis.

While negative life events (e.g. bereavement) are typically associated with severe acute stress, the PSS measures perceived chronic stress that occurs when various demands in daily life exceed an individual's coping mechanisms. It covers various aspects, including feelings of unpredictability, lack of control and overload. It is possible that the allostatic load (the cumulative 'wear and tear' on the body associated with stress) depends on the type of stress and coping mechanisms,[2] such that experiencing persistent daily stress, but not severe acute stress, may depress cell-mediated immunity and trigger VZV reactivation. This explanation is also consistent with decreased cell-mediated immunity to VZV[29,30] and increased risk of HZ in persons with mood disorders,[6,8,9,23,24] which are chronically stressful conditions.

Table 1 Distribution of cohort characteristics at baseline, Danish National Health Survey 2010–2014[a]

Baseline characteristic	n (%)
Age group (years)	
40–49	21 258 (31·2)
50–59	18 463 (27·1)
60–69	17 313 (25·4)
70–79	8008 (11·7)
≥ 80	3122 (4·6)
Sex	
Men	34 804 (51·1)
Women	33 360 (48·9)
Immunosuppressive and chronic conditions	
Rheumatoid arthritis	5044 (7·4)
Systemic lupus erythematosus	69 (0·1)
Inflammatory bowel disease	823 (1·2)
Chronic kidney disease	384 (0·6)
Asthma	1983 (2·9)
Chronic obstructive pulmonary disease	4498 (6·6)
Inhaled corticosteroids	2643 (3·9)
Diabetes	4543 (6·7)
Mood disorder	3451 (5·1)
Severe immunosuppression	1885 (2·8)
HIV	46 (0·1)
Other immunosuppressive disease	28 (0)
Leukaemia	94 (0·1)
Lymphoma	239 (0·4)
Myeloma	26 (0)
Oral corticosteroids	859 (1·3)
Haematopoietic stem cell transplant	49 (0·1)
Other immunosuppressants	763 (1·1)
Highest achieved education (years)	
Short	17 157 (25·2)
Intermediate	33 793 (49·6)
High	17 214 (25·3)
Country of origin	
Danish	63 456 (93·1)
Other Western	2469 (3·6)
Non-Western	2239 (3·3)
Smoking status	
Never	27 321 (40·1)
Former	23 903 (35·1)
Current	16 940 (24·9)
Weekly alcohol consumption	
Low risk	51 067 (74·9)
Intermediate risk	9599 (14·1)
High risk	7498 (11·0)
Body mass index category	
Underweight	1047 (1·5)
Normal	30 543 (44·8)
Overweight	25 956 (38·1)
Obese	10 618 (15·6)
Physical activity	
Sedentary	10 151 (14·9)
Light	42 270 (62·0)
Moderate	14 462 (21·2)
Vigorous	1281 (1·9)
Perceived Stress Scale score, quintiles	
0–6	15 953 (23·4)
7–10	15 718 (23·1)
11–13	11 939 (17·5)
14–17	11 943 (17·5)
≥ 18	12 611 (18·5)

[a]In all analyses, we included calibrated weights to statistically account for survey design and differential nonresponse. Thus, estimates may not add up to totals.

Strengths of our study include the population-based design in a tax-funded universal healthcare system, the use of prospectively collected data, large study size, and availability of information on important HZ risk factors, lifestyle and anthropometric factors. Although the response rate was relatively low, we believe that selection bias was limited because: (i) loss to follow-up was minor; (ii) comparisons were made internally among participants; (iii) survey weights were used to account for differential nonresponse; (iv) the presence of missing data seemed conditionally independent of our outcome (Table S4); and (v) HRs for known HZ risk factors were similar for nonresponders and the final study population (Figure S1).

Although the PSS score has been found to be valid and reliable for measuring perceived psychological stress in daily life,[19,31] misclassification is possible because of scalability issues introduced with the mix of negative and positive items.[32] Furthermore, we were unable to measure changes in PSS score during follow-up; however, PSS score has previously been found to be relatively stable over time.[33]

Our algorithm for identifying HZ is valid (positive predictive value for prescriptions = 87%) and is likely to capture the vast majority of persons with HZ treated by any physician in Denmark,[22] as healthcare access does not require copayment and costs of prescription drugs, including antivirals, are partially reimbursed. Nevertheless, some persons with HZ never seek care or seek care too late to benefit from antiviral therapy. We cannot rule out that psychological stress affects health-seeking behaviour, resulting in an increased chance of HZ diagnosis in people with higher PSS scores in our study. However, the lack of an association for the 80% of the study population who had a PSS score below 20 suggests that at least strong differential misclassification did not occur. Furthermore, our estimates were not affected by adjustment for several variables potentially associated with healthcare contacts.

We adjusted for a wide range of HZ risk factors at baseline using prospectively collected data from multiple sources. Nevertheless, residual confounding remains possible owing to incomplete data or changes in covariable status during follow-up. Furthermore, simultaneous misclassification of self-reported variables (e.g. a tendency to misreport both smoking and alcohol consumption) may have introduced bias or residual confounding that is difficult to predict.[34] However,

Table 2 Association between Perceived Stress Scale (PSS) score quintiles and herpes zoster, Danish National Health Survey 2010–2014[a]

				Hazard ratios (95% confidence interval)[b]			
PSS score	Events	Person-years	Rate (per 1000)	Model 1	Model 2	Model 3	Model 4
Score 0–6	359	64 849	5·53	Reference	Reference	Reference	Reference
Score 7–10	358	63 940	5·60	1·00 (0·87–1·16)	0·99 (0·86–1·15)	1·00 (0·86–1·16)	1·00 (0·86–1·16)
Score 11–13	302	48 193	6·26	1·09 (0·94–1·28)	1·07 (0·92–1·26)	1·08 (0·92–1·26)	1·08 (0·92–1·26)
Score 14–17	311	48 028	6·46	1·08 (0·93–1·26)	1·05 (0·89–1·22)	1·05 (0·90–1·23)	1·05 (0·90–1·23)
Score ≥ 18	357	49 635	7·20	1·21 (1·03–1·41)	1·13 (0·96–1·32)	1·13 (0·96–1·33)	1·14 (0·97–1·34)

[a]In all analyses, we included calibrated weights to statistically account for survey design and differential nonresponse. Thus, estimates may not add up to totals. [b]The underlying timescale was age. Model 1 adjusted for sex; Model 2 adjusted additionally for immunosuppressive and chronic conditions (rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic kidney disease, asthma, chronic obstructive pulmonary disease, use of inhaled corticosteroids, diabetes, mood disorder, human immunodeficiency virus infection, haematopoietic stem cell transplantation, other cellular immune deficiency, leukaemia, lymphoma, myeloma and use of oral glucocorticoids or other immunosuppressant drugs); Model 3 additionally adjusted for country of origin and education level; and Model 4 additionally adjusted for smoking status, alcohol consumption, body mass index and physical activity.

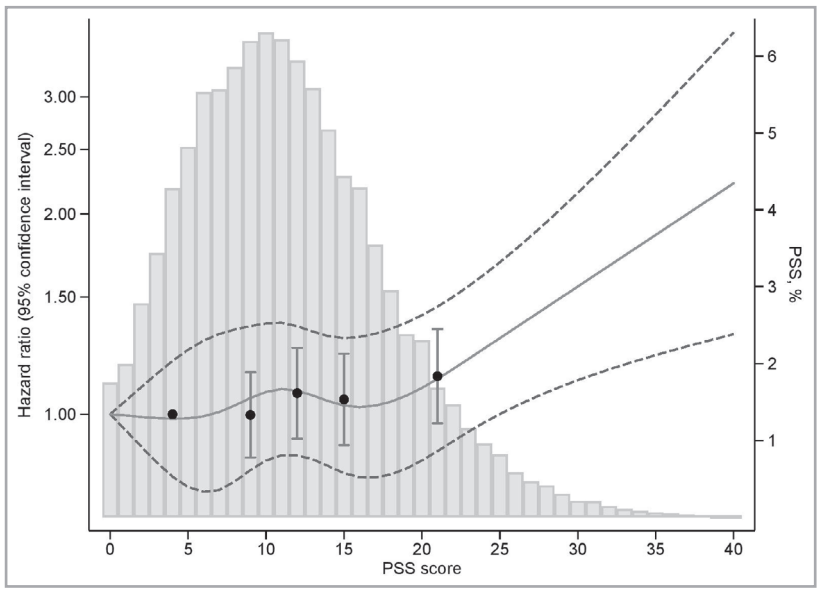

Figure 2 Fully adjusted hazard ratio[a] for herpes zoster associated with Perceived Stress Scale (PSS) score, entered as a restricted cubic spline model (solid and dashed lines) and as quintiles (circles with error bars). Grey columns represent the distribution of PSS scores (%) in the study population[a]The underlying timescale was age. Adjusted for sex, immunosuppressive and chronic conditions (rheumatoid arthritis, lupus erythematosus, inflammatory bowel disease, chronic kidney disease, asthma, chronic obstructive pulmonary disease, use of inhaled corticosteroids, diabetes, mood disorder, HIV infection, haematopoietic stem cell transplantation, other cellular immune deficiency, leukaemia, lymphoma, myeloma, and use of oral glucocorticoids or other immunosuppressant drugs), country of origin, education level, smoking status, alcohol consumption, body mass index and physical activity.

estimates remained relatively consistent across multivariable models with self-reported data.

Owing to concerns about overadjustment of the association of interest, we did not adjust for symptoms and other measures of psychological distress that may correlate with the PSS (e.g. the Short Form Health Survey).[31] We cannot rule out residual confounding by psychiatric disorder, but we note that there was no change in HRs upon adding mood disorders to the multivariable model after adjusting for other chronic diseases and sex.

Even though this is the largest study to examine the association between perceived psychological stress and risk of HZ, statistical uncertainty should be considered. Our data are most compatible with a 14% increase in the relative risk of HZ among those with a PSS score in the highest quintile, but are also reasonably compatible with a 3% decrease or a 34% increase (i.e. the lower and upper confidence limits). Subgroup analyses also should also be interpreted with caution because of wide confidence intervals.

We expect that our study findings could be generalized to populations similar to the Danish population. It is uncertain whether these findings could be extrapolated to other populations, for instance those where other ethnicities are

predominant, as it is unknown whether such factors modify the association between stress and HZ. Nevertheless, similar results were found for Japanese men.[11]

We have identified perceived psychological stress as a potential modifiable risk factor for HZ in adults aged 40 years or older. This finding is of public health importance because HZ is a common condition[35] and a considerable proportion of the population (20%) reports such high levels of stress.[21] Thus, our study adds HZ to the growing list of potential negative health consequences of psychological stress, and underscores the importance of supporting mental wellbeing and resilience in the general population.

References

1 Zorrilla EP, Luborsky L, McKay JR *et al.* The relationship of depression and stressors to immunological assays: a meta-analytic review. *Brain Behav Immun* 2001; **15**:199–226.
2 Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull* 2004; **130**:601–30.
3 Schmader K. Herpes zoster. *Ann Intern Med* 2018; **169**:ITC19–ITC31.
4 Schmidt SAJ, Vestergaard M, Pedersen HS *et al.* 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**:572–9.
5 Harpaz R, Leung JW, Brown CJ, Zhou FJ. Psychological stress as a trigger for herpes zoster: might the conventional wisdom be wrong? *Clin Infect Dis* 2015; **60**:781–5.
6 Schmader K, George LK, Burchett BM *et al.* Race and stress in the incidence of herpes zoster in older adults. *J Am Geriatr Soc* 1998; **46**:973–7.
7 Schmader K, Studenski S, MacMillan J *et al.* Are stressful life events risk factors for herpes zoster? *J Am Geriatr Soc* 1990; **38**:1188–94.
8 Lasserre A, Blaizeau F, Gorwood P *et al.* Herpes zoster: family history and psychological stress-case-control study. *J Clin Virol* 2012; **55**:153–7.
9 Marin M, Harpaz R, Zhang J *et al.* Risk factors for herpes zoster among adults. *Open Forum Infect Dis* 2016; **3**:ofw119.
10 Kim CK, Choi YM, Bae E *et al.* Reduced NK cell IFN-γ secretion and psychological stress are independently associated with herpes zoster. *PLoS One* 2018; **13**:e0193299.
11 Takao Y, Okuno Y, Mori Y *et al.* Associations of perceived mental stress, sense of purpose in life, and negative life events with the risk of incident herpes zoster and postherpetic neuralgia. *Am J Epidemiol* 2017; **187**:251–9.
12 Christensen AI, Ekholm O, Glümer C *et al.* The Danish National Health Survey 2010. Study design and respondent characteristics. *Scand J Public Health* 2012; **40**:391–7.
13 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014; **29**:541–9.
14 Fangel S, Linde PC, Thorsted BL. [New problems with survey representativity, which enumeration with registers is able to reduce]. *Metode Og Data* 2007; **93**:14–26 (in Danish).
15 Schmidt M, Schmidt SAJ, Sandegaard JL *et al.* The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015; **7**:449–90.
16 Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health* 2011; **39**:54–7.
17 Pottegård A, Schmidt SAJ, Wallach-Kildemoes H *et al.* Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol* 2017; **46**:798–798f.
18 Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health* 2011; **39**:91–4.
19 Cohen S, Williamson G. Perceived stress in a probability sample in the United States. In: *The Social Psychology of Health* (Spacapan S, Oskamp S, eds), Newbury Park, CA: Sage, 1988; 31–67.
20 Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983; **24**:385–96.
21 Nielsen L, Curtis T, Kristensen TS, Rod Nielsen N. What characterizes persons with high levels of perceived stress in Denmark? A national representative study. *Scand J Public Health* 2008; **36**:369–79.
22 Schmidt SAJ, Vestergaard M, Baggesen LM *et al.* Prevaccination epidemiology of herpes zoster in Denmark: quantification of occurrence and risk factors. *Vaccine* 2017; **35**:5589–96.
23 Schmidt SAJ, Langan SM, Pedersen HS *et al.* Mood Disorders and risk of herpes zoster in 2 population-based case-control studies in Denmark and the United Kingdom. *Am J Epidemiol* 2018; **187**:1019–28.
24 Marra F, Parhar K, Huang B, Vadlamudi N. Risk factors for herpes zoster infection: a meta-analysis. *Open Forum Infect Dis* 2020; **7**: ofaa005.
25 Jain A, van Hoek AJ, Walker JL *et al.* Inequalities in zoster disease burden: a population-based cohort study to identify social determinants using linked data from the U.K. Clinical Practice Research Datalink. *Br J Dermatol* 2018; **178**:1324–30.
26 Cox DR. Regression models and life-tables. *J Roy Stat Soc B* 2010; **34**:187–220.
27 Gauthier J, Wu QV, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. *Bone Marrow Transpl* 2020; **55**:675–80.
28 Bartlett JW, Harel O, Carpenter JR. Asymptotically unbiased estimation of exposure odds ratios in complete records logistic regression. *Am J Epidemiol* 2015; **182**:730–6.
29 Irwin M, Costlow C, Williams H *et al.* Cellular immunity to varicella-zoster virus in patients with major depression. *J Infect Dis* 1998; **178** (Suppl. 1):S104–S108.
30 Irwin MR, Levin MJ, Carrillo C *et al.* Major depressive disorder and immunity to varicella-zoster virus in the elderly. *Brain Behav Immun* 2011; **25**:759–66.
31 Lee E-H. Review of the psychometric evidence of the perceived stress scale. *Asian Nurs Res (Korean Soc Nurs Sci)* 2012; **6**:121–7.
32 Nielsen MG, Ørnbøl E, Vestergaard M *et al.* The construct validity of the Perceived Stress Scale. *J Psychosom Res* 2016; **84**:22–30.
33 Barbosa-Leiker C, Kostick M, Lei M *et al.* Measurement invariance of the perceived stress scale and latent mean differences across gender and time. *Stress Health* 2013; **29**:253–60.
34 Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. In: *Modern Epidemiology* (Rothman KJ, Greenland S, Lash TL, eds), 3rd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2008; 128–47.
35 Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open* 2014; **4**:e004833.

Appendix

All authors participated in the design of the study. S.A.J.S. had access to and analysed the data and wrote the initial manuscript draft. All authors participated in the discussion and interpretation of the results, critically revised the manuscript for intellectual content, and approved the final version. S.A.J.S. is the guarantor.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Additional description of the Danish National Health Survey and databases used in the study.

Figure S1 Directed acyclic graph illustrating the conceptual framework for the association between perceived stress and herpes zoster.

Figure S2 Hazard ratios (95% confidence intervals) associated with study covariables based on routinely collected registry data among survey nonresponders (n = 68 044) and among persons in final study population (n = 77 310).

Table S1 Code lists for exposures, outcomes and covariables.

Table S2 Distribution of variables prior to excluding those with missing data.

Table S3 Characteristics by missingness overall, for Perceived Stress Scale (PSS) score and for lifestyle and anthropometric factors.

Table S4 Odds ratios (95% confidence intervals) for missingness associated with study variables overall, for Perceived Stress Scale (PSS) score and for lifestyle and anthropometric factors.

Table S5 Cohort characteristics at start of follow-up stratified by Perceived Stress Scale score.

Table S6 Fully adjusted hazard ratios (95% confidence intervals) for the association between Perceived Stress Scale (PSS) score and herpes zoster, by age and sex.