Supplementary Appendix

eMethods 1. Directed acyclic graph for the study on herpes zoster and risk of dementia, including description of study hypotheses and rationale for covariables included

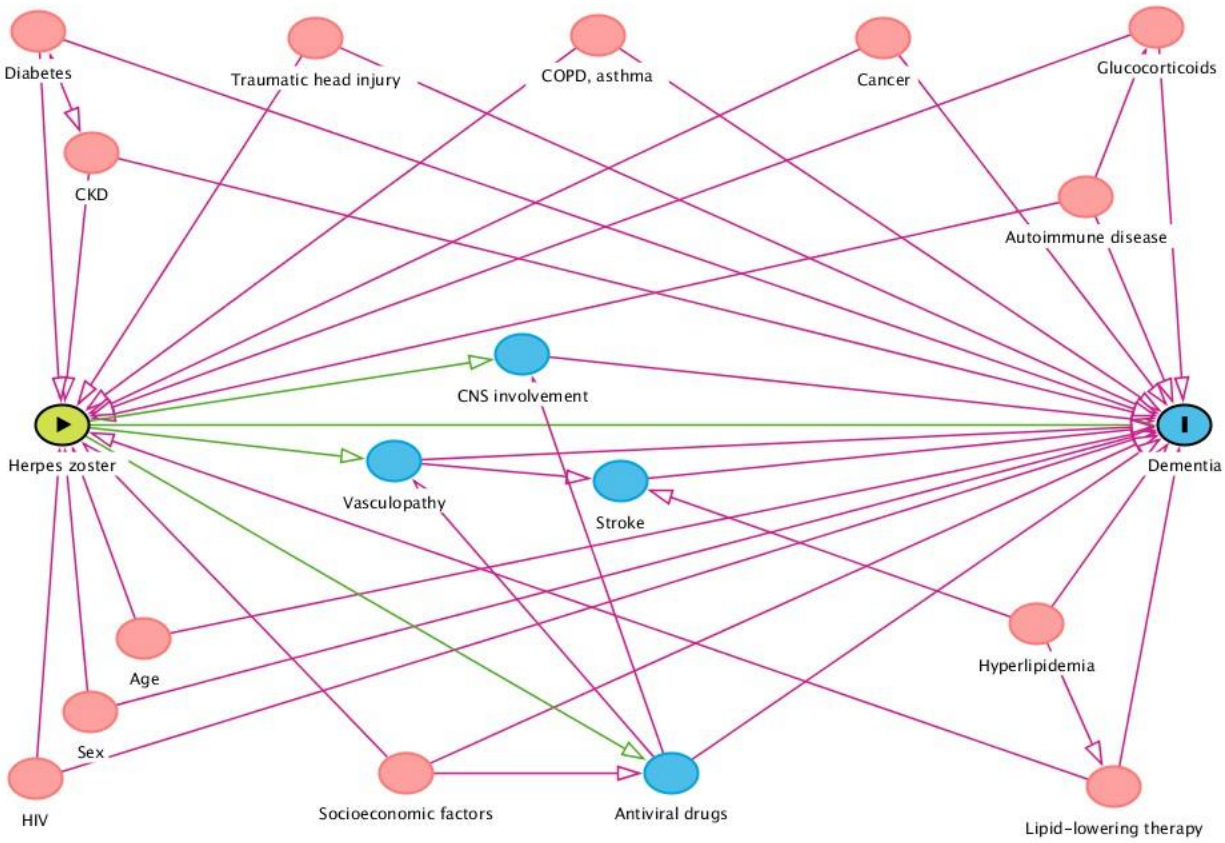

Figure. Directed acyclic graph for the study.
Abbreviations: CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus

Hypotheses for association:

1. HZ → neuroinflammation → dementia (this is illustrated as the direct effect in the Figure)
2. HZ → (cerebral) vasculopathy → stroke → dementia[1-3] (vasculopathy could also lead to neurodegeneration without clinically apparent stroke)

3. HZ → Central nervous system (CNS) complications (encephalitis) → dementia[4,5]

Proposed mechanism 2 and 3 could be most pronounced for HZ involving cranial nerves or CNS. Thus, stroke and HZ involving cranial nerves and CNS may act as mediators, which we explore in our subgroup analyses. In addition to these pathways, antiviral treatment for HZ may modify dementia risk, as also shown in the DAG, by decreasing viral replication and risk of complications, such as CNS involvement and stroke. However, evidence for short-term antiviral treatment and risk of dementia is limited.[6] Unfortunately, we do not have sufficient data to examine antiviral treatment as an effect modifier, but note that almost all patients in our cohort will have received antivirals and therefore our results reflect the risk of dementia in treated HZ.

Confounders/mediators

- Age: strong risk factor for both HZ[4,7] and dementia.[8]
- Sex
- Traumatic head injury: Increased risk of HZ[9,10] and dementia. [7,10]
- Autoimmune diseases: Increased risk of HZ[7] and has been associated with dementia (especially for severe autoimmune disease).[11,12]
- Glucocorticoids: Oral glucocorticoids are associated with increased risk of HZ[4] and may reduce dementia risk.[12,13]
- Diabetes: May be associated with increased risk of HZ[7] and also dementia (perhaps mediated through stroke).[7,10,14]
- Chronic obstructive pulmonary disease (COPD) and asthma: Have been associated with increased risk of HZ[7] and may be associated with dementia (*e.g.*, through harmful effects of low oxygen and high carbon dioxide levels and for COPD through smoking), although evidence is conflicting.[14-16]

- Chronic kidney disease: Associated with increased risk of HZ[7] and possibly of dementia[17] (perhaps mediated through stroke).
- Hyperlipidemia and lipid-lowering therapy: Association between cholesterol levels hand HZ has not been examined directly, but statins are associated with increased risk (increases with increasing dose/potency).[18] Hyperlipidemia is also associated with dementia risk,[17] although statins do to prevent dementia in older people at risk of vascular disease.
- HIV: Increased risk of HZ[7] and dementia.[19]
- Cancer: Cancer, in particular hematological cancer, is a risk factor for zoster (even in occult stage[20-22] and has also been associated with dementia, although evidence is controversial.[23,24]

Other variables:

- Depression/mood disorder: Moderate-to-severe depression and other mood disorders have been associated with increased risk of HZ[7] and HZ also increases risk of depression. Thus, mood disorders could act as confounders or mediators. However, the association with dementia is unclear, as most analyses are based on midlife depression, at which time pathological changes of dementia may already be underway. Thus, depressive symptoms could be an early sign (*i.e.*, early misdiagnosis), [7,10] resulting in misclassification with the outcome. We therefore decided not to include depression/mood disorder as a potential confounder or mediator.
- HZ has been associated with increased risk of coronary heart disease,[1,25] which in turn has been associated with dementia.[26] Part of this effect is thought to be mediated through hyperlipidemia and depression. To avoid potential misclassification we have not adjusted for depression (see above).
- We have not found evidence linking HZ to apolipoprotein E-4 or hypertension, and have therefore not included hypertension as a relevant confounder or mediator.

- We have not found that other risk factors for HZ, including *e.g.* hematopoietic stem cell transplantation and other cellular immune deficiency, are important risk factors for dementia.
- Lifestyle, anthropometric and socioeconomic factors may predict risk for dementia.[10,27] However, in a study on lifestyle and anthropometric factors, we found that smoking status, alcohol consumption, body mass index, and physical activity were not associated with increased HRs for HZ.[27] Thus, we are not concerned about unmeasured confounding by these factors. Regardless, we do include adjustment for several lifestyle-related diseases, which partly accounts for any impact of these factors.
- Low socioeconomic status is associated with increased risk of dementia[10,27] and an increased risk of HZ diagnosis in some settings.[28,29] It could also affect probability of treatment for HZ. However, in a Danish survey-based study, we did not find evidence that educational level, working status, and civil/partnership status were risk factors of HZ.[27] Similarly, a multicenter study, including data from Denmark, on antivirals for herpes infections and risk of dementia also found that adjustment for socioeconomic factors had no impact on results. [6] We are therefore not concerned of confounding by such factors, but have included in the DAG nevertheless to account for potential uncertainty on this matter.

Conclusion regarding adjustments

Based on the graph, the minimal sufficient adjustment set for estimating the 'total effect' is age, sex, autoimmune disease, chronic kidney disease, chronic pulmonary disease, asthma, cancer, diabetes, glucocorticoids, HIV, lipid-lowering therapy, and traumatic head injury. Adjustment for socioeconomic variables would also be required; however, please see above about evidence suggesting this is not an important confounder. To estimate the 'direct effect' would additionally require adjustment for CNS involvement, vasculopathy and antivirals (see above).

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eMethods 2. Code lists for exposures, outcomes, and covariables in the study on herpes zoster and risk of dementia

Definitions of exposure (herpes zoster)

Type of record	Registry codes
Hospital diagnoses of herpes zoster	ICD-8: 053; ICD-10: B02, G051I, G051M, H031F, H131M, H190D, H192D, H192J, H220C, H621B
Codes specifying herpes zoster in dermatomes corresponding to cranial nerves	ICD-10: B023, H031F, H131M, H190D, H192D, H192J, H220C, H621B *or* if code DB02 is used in combination with one of the following during the same hospital contact (correspond to more unspecific codes stating inflammation in various structures of eye and external ear due to an unspecified infection, as well as codes for affection of cranial nerves. Unspecific codes for inflammation where infection was not stated as reason were not included, e.g. blepharitis, keratitis, uveitis and iridocyclitis without further specification): H031, H131, H190, H192, H220, H621, G509, G510, DG518C, G518D, G519, H490, H491, H492
Codes specifying herpes zoster with encephalitis/meningoencephalitis/ meningitis/myelitis	ICD-10: B020, B021, G051I, G051M *or* if code B02 is used in combination with one of the following during the same hospital contact (correspond to more unspecific codes for encephalitis/meningitis/encephalomyelitis/myelitis): G051U, G051V, G051X
Antiviral treatment in general practice	
Acyclovir	ATC code: J05AB01; Zoster specific doses (800 mg in packages of 35 pills) identified by requiring variable packsize to be ’35’ and strnum to be ‘800’
Valacyclovir	ATC code: J05AB11; Zoster specific doses (500 mg tablet doses) identified by requiring variable strnum to be ‘500’
Famciclovir	ATC code: J05AB09; Zoster specific doses (500 mg tablet doses) identified by requiring variable strnum to be ‘500’
Hospital diagnoses of postherpetic neuralgia	ICD-10: G530

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

Subcodes included unless otherwise stated.

Definitions of outcome (dementia)

Type of record	Registry codes
All-cause dementia	All codes listed below
Alzheimer's disease	ICD-8: 29009, 29010 ICD-10: F00, G30 (includes G30, G300, G301, G308, G309)
Vascular dementia (not included as separate category)	ICD-8: 29309, 29319 ICD-10: F01 (includes F010x, F011x, F012x, F013x, DF018X, F019x)
Other dementia (not included as separate category)	ICD-8: 09419, 29209, 29011, 29018, 29019 ICD-10: F02, F03, F1x73 (F1073 through F1973); G231; G310, G311, G318B, G318E
Drugs used for dementia (excluded in sensitivity analysis)	ATC: N06D
Alzheimer's disease in sensitivity analysis	ICD-8: 29009, 29010 ICD-10: F00, F03, G30 (includes G30, G300, G301, G308, G309)
Mild cognitive impairment and amnestic syndromes (not used to identify incidence dementia)	ICD-8: 29119 ICD-10: F04, F049, F051, F067 and F067x, F1x6 (F106, F186, F196)
Codes indicating Parkinson's disease or Lewy body dementia (for sensitivity analysis)	ICD-8; 342 ICD-10: F023, G20, G318E ATC code: N04BA, N04BC

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

Subcodes included unless otherwise stated.

Definitions of covariables

Variable	Definition	Codes
Traumatic head injury	– Any diagnosis in the DNPR prior to index date – Includes severe injuries, such as, brain concussion, skull fractures (not facial and tooth fractures), crushing injuries to head, intracranial contusions and/or hemorrhages, and multiple lesions to head)	– ICD-8: 800, 801, 803, 851, 852, 853, 854 – ICD-10: S020, S021, S027, S028, S029, S06, S07, S097
Oral glucocorticoids	– Any record in the	– H02AB (excluding injections by

	Prescription Registry within 90 days before start of follow-up	limiting to prescriptions where variable packtext ends with “stk” “stk.” or “(blister)”)
Diabetes mellitus	– Any previous diagnosis in DNPR *or* – ≥2 prescriptions for antidiabetics in Prescription Registry (except women treated with metformin alone at age 20 to 39 years, as that may represent treatment of polycystic ovarian syndrome)	– ICD-8: 249, 250 – ICD-10: E10; E11; E12; E13; E14; H360; O24 (excluding O244) – ATC: A10A, A10B, B04AX07, C10AX04 (excluding A10BE01**)**
Chronic obstructive pulmonary disease	– Any previous diagnosis in the DNPR *and* – ≥35 years at first diagnosis	– ICD-8: 491, 492 – ICD-10: J41, J42, J43, J44
Active asthma	– Any previous diagnosis in the DNPR *and* – Asthma prescription in the Prescription Registry in the year before follow-up start *and* – No previous COPD defined as in previous variable	– ICD-8: 493 – ICD-10: J45, J46 – ATC: R03
Chronic kidney disease	– Any previous record of chronic kidney disease stage 3 or higher, renal failure, chronic uremia, dialysis or renal transplantation in the DNPR	– ICD-8: 584, 792, 9977, Y9509 – ICD-10: L298C, G638A, E853B, T825A, T825B, T825C, T856C, I120, I131, I132, I770, N165, N180, N183, N184, N185, N188, N189, N19, T824, T861, Z49, Z94, Z992, T817E1 – Danish surgical codes (old classification; c_opr/c_tilopr): 57480; 57490; 87409; 87419; 87420; 87430; 87431; 87432; 87440; 92390; 92400; 94300; 94340 – NOMESCO classification surgery

		codes (c_opr/c_tilopr): KJAK10, KJAK11, KJAK13, KJAK14, KTJA30, KTJA32, KTJA35, KKAS – Treatment codes (c_opr/c_tilopr): BJFD2, BJFZ, BJKB, BUFC1, BWDC5, ZZ0151A, ZZ4341, ZZ4342, ZZ4343, ZZ4346, ZZ4347, ZZ4348, ZZ4350
Hyperlipidemia and lipid-lowering therapy	– Any previous diagnosis in DNPR *or* – A record for lipid-lowering therapy in Prescription Registry	– ICD-8: 27200, 27201 – ICD-10: E780, E781, E782, E783, E784, E785 – ATC: C10, B04A
Human immunodeficiency virus infection	– Any previous diagnosis in the DNPR	– ICD-8: 07983, Y4049, Y4149 – ICD-10: B20, B21, B22, B23, B24, Z21
Hematological cancer	– Any previous diagnosis in the DCR before start of follow-up	– ICD-8: 200, 201, 202, 203, 204, 205, 206, 207 – ICD-10: C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C95, C96
Solid cancer	– Any previous diagnosis in the DCR before start of follow-up	– ICD-8: 140–199, 27559 – ICD-10: C00–C80
Stroke	– Any previous diagnosis in the DNPR before start of follow-up or during follow-up (time-varying)	– ICD-8: 430, 431, 433, 434 – ICD-10: I60, I61, I63, I64
Acute myocardial infarction	– Any previous diagnosis in the DNPR	– ICD-8: 410 – ICD-10: I21
Angina pectoris	– Any previous diagnosis in the DNPR	– ICD-8: 413, 411 – ICD-10: I20, I251, I259
Heart failure	– Any previous diagnosis in the DNPR	– ICD-8: 42709, 42710, 42711, 42719, 42899, 78249 – ICD-10: I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429
Hypertension or treatment with antihypertensives	– Any previous diagnosis in the	– ICD-8: 400-404 – ICD-10: I10-I15

	DNPR – A prescription for combination antihypertensive tablets or at least prescriptions for two different antihypertensive drugs	– ATC for antihypertensive tablets: C02DE52, C02LM01–C02LM08, C02LM12, C07BA06, C07CA03, C07CB03, C07CB03, C07FB02, C08CA55, C08DA51, C09BA, C09BB, C09DA, C09DB – ATC for different antihypertensive drugs: C02DF01, C02EA, C02EX01, C03, C07, C08, C09AA, C09CA
Liver disease	– Any of the codes listed below	– ICD-8: 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09, 571, 573.01, 573.04 ICD-10: B15.0, B16.0, B16.2, B19.0 B18, I85, K70.0-K70.3, K70.4, K70.9, K71, K72, K73, K74, K76.0, K76.6,
Haematological system		
Autoimmune haemolytic anaemia		– ICD-8: 28390 – ICD-10: 590, 591
Idiopathic thrombocytopenic purpura		– ICD-8: 28710 – ICD-10: 693
Endocrine system		
Graves' disease		– ICD-8: 24200, 24201, 24208, 24209 – ICD-10: E05.0
Autoimmune thyroiditis		– ICD-8: 24401, 24503 – ICD-10: E06.3
Addison´s disease		– ICD-8: 25510; – ICD-10: E27.1
Diabetes type I		– ICD-8: 249 – ICD-10: E10
Central nervous/ neuromuscular system		
Multiple sclerosis		– ICD-8: 340 – ICD-10: G35
Myasthenia gravis		– ICD-8: 73309 – ICD-10: G700
Gastrointestinal/hepatobiliary system		
Pernicious anemia		– ICD-8: 28100, 28101, 28108, 28109 – ICD-10: D510
Coeliac disease		– ICD-8: 26900 – ICD-10: K900
Crohn´s disease		– ICD-8: 56301, 56302, 56309 – ICD-10: K50, M074
Ulcerative colitis		– ICD-8: 56319, 56904 – ICD-10: K51, M075
Primary biliary cirrhosis		– ICD-8: 57190

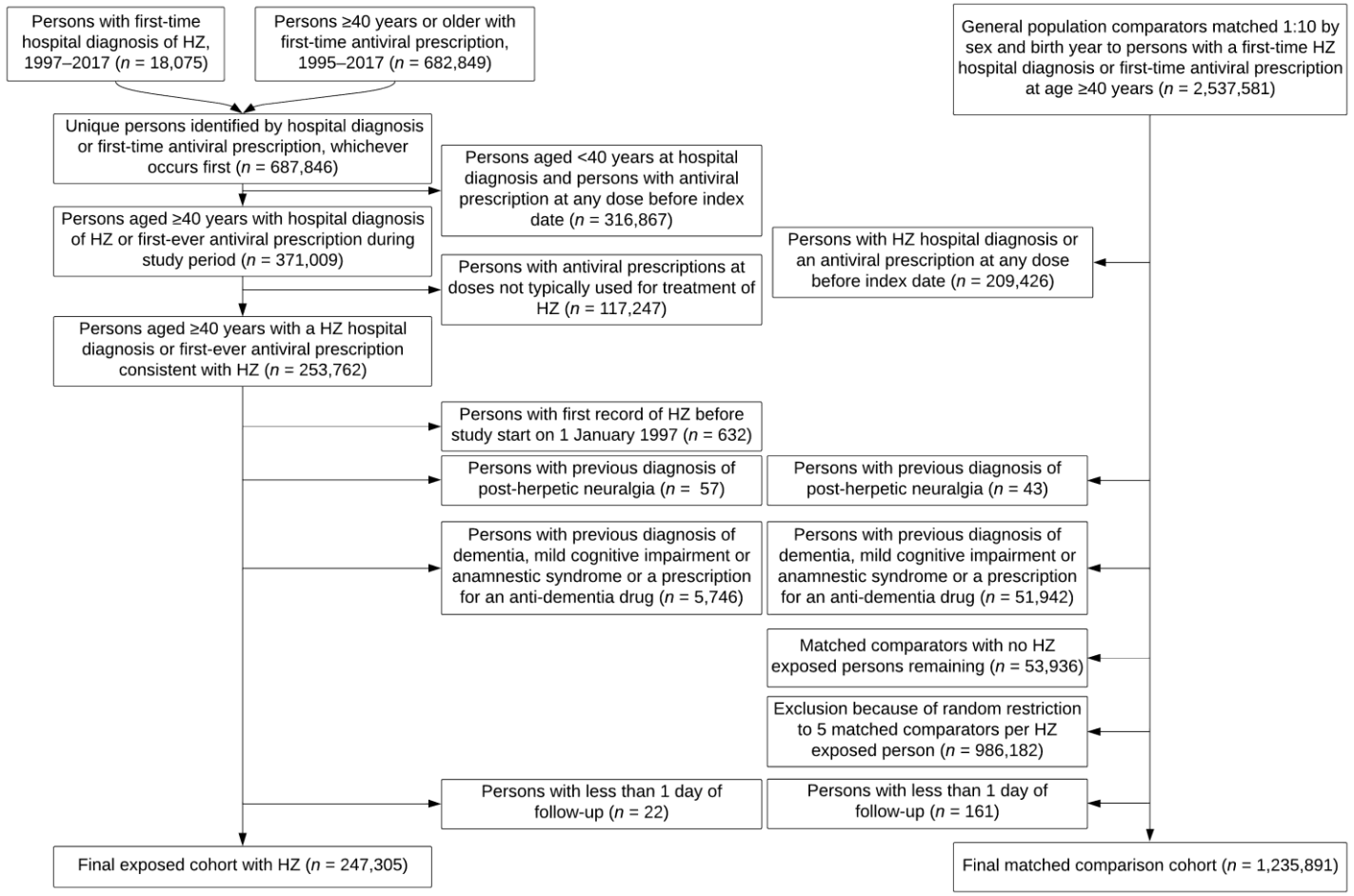
	– ICD-10: K743
Skin	
Atopic dermatitis	– ICD-8: 69100 – ICD-10: L20
Pemphigus/pemphigoid	– ICD-8: 69400, 69401, 69402, 69403, 69405 – ICD-10: L100, L101, L102, L104, L120
Dermatitis herpetiformis	– ICD-8: 69308, 69309 – ICD-10: L130
Psoriasis	– ICD-8: 69609, 69610, 69619 – ICD-10: L40, M070, M071, M072, M073
Vitiligo	– ICD-8: 70901 – ICD-10: L80
Connective tissue diseases	
Rheumatoid arthritis	– ICD-8: 71219, 71229, 71239, 71259 – ICD-10: M05, M06, G737D, I328A, I398E, I418A, I528A
Juvenile arthritis	– ICD-8: 71209 – ICD-10: M08, M09
Ankylosing spondylitis	– ICD-8: 71249 – ICD-10: M45, H221B
Polymyositis/dermatomyositis	– ICD-8: 71609, 71619 – ICD-10: M33
Systemic- and subacute cutaneous lupus erythematosus	– ICD-8: 73419 – ICD-10: M32, G058A, G737C, I328B, I398C, L931, L932, N085A, N164B
Systemic scleroderma	– ICD-8: 73400, 73401, 73402, 73403, 73404, 73405, 73406, 73407, 73408, 73409; – ICD-10: M34
Mixed connective tissue disease	– ICD-8: 73491 – ICD-10: M351
Sjögren´s syndrome	– ICD-8: 73490; – ICD-10: M350, G737A, N164A
Sarcoidosis	– ICD-8: 13599 – ICD-10: D86, G532, H221A, I418B, K778B, M633
Vasculitis syndromes including polymyalgia rheumatica	– ICD-8: 28709, 44609-44699 – ICD-10: D690B, I776, L95, M30, M31, M353, M356, DM793, N085B, N085C, N085D, DN085E
Pulmonary system	
Idiopathic fibrosing	– ICD-8: 51701

alveolitis (pulmonary fibrosis)	– ICD-10: J841A, J841B, J841C
Ocular diseases	
Iridocyclitis	– ICD-8: 364 – ICD-10: H200, H201

Abbreviations: ATC=Anatomical Therapeutic Chemical Classification System; DCR=Danish Cancer Registry; DNPR= Danish National Patient Registry; ICD=International Classification of Disease; NOMESCO=Nordic Medico-Statistical Committee

Subcodes included unless otherwise stated. The diagnosis date was the date of admission or first outpatient contact for diagnoses and date of prescription for drugs.

eFigure 1. Study flowchart



Abbreviations: HZ = herpes zoster

Note: The initial sampling of exposed persons and matched comparators was performed as part of a large project on the epidemiology of HZ. Up to 10 comparators were selected for each HZ patient in order to ensure sufficient numbers for the different projects included. For the current study on dementia, we restricted to 5 matched comparators per HZ patients.

eTable 1. Number of events, accumulated person-time, rates, and HRs of dementia associated with a previous diagnosis of HZ, Denmark 1997–2017

	HZ				Comparison cohort				HR (95% CI)		
	No. of persons	**No. of events**	**Person-years at risk**	**Rate per 1,000 person-years (95% CI)**	**No. of persons**	**No. of events**	**Person-years at risk**	**Rate per 1,000 person-years (95% CI)**	**Unadjusted[a]**	**Confounder-adjusted, model[b]**	**Mediation model[c]**
0–1 years of follow-up	**247305**	**1238**	**233268**	**5.31 (5.01–5.60)**	**1235891**	6332	1172114	5.40 (5.27–5.54)	0.99 (0.93–1.05)	0.98 (0.92–1.04)	0.98 (0.92–1.04)
HZ involving cranial nerves	1189	18	-	16.67 (8.97–24.38)	5940	57	5600	10.18 (7.54–12.82)	1.76 (1.02–3.02)	1.83 (1.03–3.25)	1.91 (1.06–3.43)
HZ with CNS involvement	254	5	-	23.38 (2.89–43.87)	1275	7	-	5.94 (1.54–10.34)	3.98 (1.21–13.07)	6.83 (1.23–37.97)	6.59 (1.17–37.19)
Age group (years) at index date											
40–49	41077	<5	-	0.05 (-0.02–0.12)	205368	34	197399	0.17 (0.11–0.23)	0.29 (0.07–1.21)	0.00 (0.00–.)	0.00 (0.00–.)
50–59	56811	<15	-	0.22 (0.10–0.35)	284028	132	272607	0.48 (0.40–0.57)	0.45 (0.25–0.82)	0.34 (0.17–0.66)	0.33 (0.16–0.66)
60–69	61939	69	59079	1.17 (0.89–1.44)	309662	461	296506	1.55 (1.41–1.70)	0.75 (0.58–0.97)	0.66 (0.51–0.86)	0.65 (0.50–0.85)
70+	87478	1155	80192	14.40 (13.57–15.23)	436833	5705	405602	14.07 (13.70–14.43)	1.02 (0.96–1.09)	1.02 (0.96–1.09)	1.02 (0.96–1.09)
Sex											
Women	149796	783	141673	5.53 (5.14–5.91)	748427	4037	710471	5.68 (5.51–5.86)	0.98 (0.91–1.06)	0.97 (0.90–1.05)	0.97 (0.90–1.05)
Men	97509	455	91596	4.97 (4.51–5.42)	487464	2295	461643	4.97 (4.77–5.17)	1.00 (0.91–1.11)	1.00 (0.90–1.11)	0.99 (0.90–1.10)
HZ identification											
Hospital-based	9027	118	7951	14.84 (12.16–	45107	361	42539	8.49 (7.61–9.36)	1.82 (1.47–2.25)	1.78 (1.42–2.23)	1.75 (1.39–2.19)

				17.52)							
Prescription-based	238278	1120	225318	4.97 (4.68–5.26)	1190784	5971	1129575	5.29 (5.15–5.42)	0.94 (0.88–1.01)	0.94 (0.88–1.00)	0.94 (0.88–1.00)
Stroke											
No	235251	1048	222506	4.71 (4.42–5.00)	1182261	5490	1123315	4.89 (4.76–5.02)	0.97 (0.91–1.04)	0.97 (0.90–1.04)	0.97 (0.90–1.04)
Yes	12054	190	10763	17.65 (15.14–20.16)	53630	842	48799	17.25 (16.09–18.42)	1.49 (1.07–2.08)	1.53 (1.09–2.15)	1.53 (1.09–2.15)
1–21 years of follow-up	**220654**	**9283**	**1532456**	**6.06 (5.93–6.18)**	**1109520**	**48602**	**7459618**	**6.52 (6.46–6.57)**	**0.93 (0.91–0.95)**	**0.93 (0.90–0.95)**	**0.92 (0.90–0.95)**
HZ involving cranial nerves	998	67	-	10.26 (7.81–12.72)	5269	316	35128	9.00 (8.00–9.99)	1.05 (0.78–1.41)	1.07 (0.79–1.45)	1.06 (0.78–1.44)
HZ with CNS involvement	190	9	-	8.77 (3.04–14.51)	1084	44	-	7.27 (5.12–9.42)	1.50 (0.67–3.35)	1.94 (0.78–4.80)	1.93 (0.78–4.80)
Age group (years) at index date											
40–49	38017	<100	-	0.32 (0.25–0.38)	189482	433	1486957	0.29 (0.26–0.32)	1.07 (0.85–1.33)	1.03 (0.82–1.30)	1.02 (0.80–1.28)
50–59	52219	<465	-	1.06 (0.97–1.16)	261264	2312	2095873	1.10 (1.06–1.15)	0.95 (0.86–1.06)	0.93 (0.84–1.03)	0.93 (0.84–1.03)
60–69	56363	1810	404094	4.48 (4.27–4.69)	283283	8923	1973682	4.52 (4.43–4.61)	0.98 (0.93–1.03)	0.97 (0.92–1.02)	0.97 (0.91–1.02)
70+	74055	6914	387005	17.87 (17.44–18.29)	375491	36934	1903105	19.41 (19.21–19.61)	0.91 (0.89–0.94)	0.91 (0.89–0.94)	0.91 (0.88–0.94)
Sex											
Women	134272	6257	947985	6.60 (6.44–6.76)	673090	31781	4570361	6.95 (6.88–7.03)	0.95 (0.92–0.98)	0.95 (0.92–0.97)	0.94 (0.92–0.97)
Men	86382	3026	584471	5.18 (4.99–5.36)	436430	16821	2889257	5.82 (5.73–5.91)	0.89 (0.85–0.93)	0.89 (0.85–0.92)	0.89 (0.85–0.92)
HZ identification											
Hospital-based	7216	392	42005	9.33 (8.41–10.26)	39947	2374	256734	9.25 (8.87–9.62)	1.09 (0.97–1.23)	1.07 (0.94–1.21)	1.04 (0.92–1.18)
Prescription-based	213438	8891	1490451	5.97 (5.84–6.09)	1069573	46228	7202884	6.42 (6.36–6.48)	0.92 (0.90–0.95)	0.92 (0.90–0.94)	0.92 (0.90–0.94)
Stroke											

No	210886	8590	1486391	5.78 (5.66–5.90)	1065185	45318	7258931	6.24 (6.19–6.30)	0.92 (0.90–0.95)	0.92 (0.90–0.94)	0.92 (0.90–0.94)
Yes	9768	693	46064	15.04 (13.92–16.16)	44335	3284	200687	16.36 (15.80–16.92)	1.03 (0.82–1.30)	1.04 (0.82–1.32)	1.04 (0.82–1.32)

Notes: In accordance with data protection rules, counts <5 are not shown.
Abbreviations: CI = confidence interval; HR = hazard ratio; HZ = herpes zoster
[a]Calculated with stratified Cox proportional hazards regression adjusted by design for birth and sex.
[b]Adjusted additionally for autoimmune disease, chronic kidney disease, chronic pulmonary disease, asthma, cancer, diabetes, glucocorticoids, human immunodeficiency virus, lipid-lowering therapy, and traumatic head injury.
[c]Adjusted additionally for time-varying stroke.

eTable 2. Number of events, accumulated person-time, rates, and HRs of dementia associated with a previous diagnosis of ophthalmic HZ, Denmark 1997–2017

	HZ				Comparison cohort				HR (95% CI)		
	No. of persons	**No. of events**	**Person-years at risk**	**Rate per 1,000 person-years (95% CI)**	**No. of persons**	**No. of events**	**Person-years at risk**	**Rate per 1,000 person-years (95% CI)**	**Unadjusted[a]**	**Confounder-adjusted, model[b]**	**Mediation model[c]**
0–1 years of follow-up	991	15	899	16.69 (8.24–25.13)	4950	49	4645	10.55 (7.60–13.50)	1.66 (0.92–2.99)	1.70 (0.91–3.17)	1.69 (0.90–3.17)
1–21 years of follow-up	829	62	5441	11.40 (8.56–14.23)	4349	264	29221	9.03 (7.94–10.12)	1.20 (0.88–1.65)	1.23 (0.89–1.70)	1.22 (0.89–1.69)

Abbreviations: CI = confidence interval; HR = hazard ratio; HZ = herpes zoster

[a]Calculated with stratified Cox proportional hazards regression adjusted by design for birth and sex.

[b]Adjusted additionally for autoimmune disease, chronic kidney disease, chronic pulmonary disease, asthma, cancer, diabetes, glucocorticoids, human immunodeficiency virus, lipid-lowering therapy, and traumatic head injury.

[c]Adjusted additionally for time-varying stroke.

eTable 3. Number of events, accumulated person-time, rates, and HRs of Alzheimer's disease associated with a previous diagnosis of HZ, Denmark 1997–2017.

	HZ				Comparison cohort				HR (95% CI)		
	No. of persons	**No. of events**	**Person-years at risk**	**Rate per 1,000 person-years (95% CI)**	**No. of persons**	**No. of events**	**Person-years at risk**	**Rate per 1,000 person-years (95% CI)**	**Unadjusted[a]**	**Confounder-adjusted, model[b]**	**Mediation model[c]**
0–1 years of follow-up	247305	418	233269	1.79 (1.62–1.96)	1235891	2336	1172114	1.99 (1.91–2.07)	0.91 (0.82–1.01)	0.91 (0.82–1.01)	0.91 (0.82–1.01)
1–21 years of follow-up	220654	3993	1532456	2.61 (2.52–2.69)	1109520	20632	7459618	2.77 (2.73–2.80)	0.93 (0.90–0.97)	0.93 (0.90–0.97)	0.93 (0.90–0.97)

Abbreviations: CI = confidence interval; HR = hazard ratio; HZ = herpes zoster

[a]Calculated with stratified Cox proportional hazards regression adjusted by design for birth and sex.

[b]Adjusted additionally for autoimmune disease, chronic kidney disease, chronic pulmonary disease, asthma, cancer, diabetes, glucocorticoids, human immunodeficiency virus, lipid-lowering therapy, and traumatic head injury.

[c]Adjusted additionally for time-varying stroke.

eTable 4. Number of events, accumulated person-time, rates, and HRs of dementia associated with a previous diagnosis of HZ, Denmark, 1997–2017, by length of follow-up.

A) Including first year of follow-up

	HZ				Comparison cohort				HR (95% CI)		
	No. of persons	No. of events	Person-years at risk	Rate per 1,000 person-years (95% CI)	No. of persons	No. of events	Person-years at risk	Rate per 1,000 person-years (95% CI)	Unadjusted[a]	Confounder-adjusted, model[b]	Mediation model[c]
All-cause dementia											
0–1 years	247305	1238	233269	5.31 (5.01–5.60)	1235891	6332	1172113.80	5.40 (5.27–5.54)	0.99 (0.93–1.05)	0.98 (0.92–1.04)	0.98 (0.92–1.04)
0–5 years	247305	4904	946330	5.18 (5.04–5.33)	1235891	27435	4721181.79	5.81 (5.74–5.88)	0.91 (0.88–0.93)	0.90 (0.87–0.93)	0.90 (0.87–0.93)
0–10 years	247305	8169	1463390	5.58 (5.46–5.70)	1235891	44258	7221836.81	6.13 (6.07–6.19)	0.92 (0.89–0.94)	0.91 (0.89–0.93)	0.91 (0.89–0.93)
0–15 years	247305	9998	1697412	5.89 (5.77–6.01)	1235891	52403	8319694.54	6.30 (6.24–6.35)	0.94 (0.92–0.96)	0.93 (0.91–0.95)	0.93 (0.91–0.95)
0–21 years	247305	10521	1765724	5.96 (5.84–6.07)	1235891	54934	8631731.68	6.36 (6.31–6.42)	0.94 (0.92–0.96)	0.93 (0.91–0.95)	0.93 (0.91–0.95)
Alzheimer's disease											
0–1 years	247305	418	233269	1.79 (1.62–1.96)	2336	1172114	1.99 (1.91–2.07)	0.91 (0.82–1.01)	0.91 (0.82–1.01)	0.91 (0.82–1.01)	0.91 (0.82–1.01)
0–5 years	247305	1848	946330	1.95 (1.86–2.04)	10556	4721182	2.24 (2.19–2.28)	0.88 (0.83–0.92)	0.88 (0.84–0.93)	0.88 (0.84–0.93)	0.88 (0.84–0.93)
0–10 years	247305	3288	1463390	2.25 (2.17–2.32)	17787	7221837	2.46 (2.43–2.50)	0.90 (0.87–0.94)	0.91 (0.87–0.94)	0.91 (0.87–0.95)	0.91 (0.87–0.95)
0–15 years	247305	4124	1697412	2.43 (2.36–2.50)	21659	8319695	2.60 (2.57–2.64)	0.93 (0.89–0.96)	0.93 (0.90–0.96)	0.93 (0.90–0.96)	0.93 (0.90–0.96)
0–21 years	247305	4411	1765724	2.50 (2.42–2.57)	22968	8631732	2.66 (2.63–2.70)	0.93 (0.90–0.96)	0.93 (0.90–0.96)	0.93 (0.90–0.96)	0.93 (0.90–0.96)

Abbreviations: CI = confidence interval; HR = hazard ratio; HZ = herpes zoster

[a]Calculated with stratified Cox proportional hazards regression adjusted by design for birth and sex.

[b]Adjusted additionally for autoimmune disease, chronic kidney disease, chronic pulmonary disease, asthma, cancer, diabetes, glucocorticoids, human immunodeficiency virus, lipid-lowering therapy, and traumatic head injury.
[c]Adjusted additionally for time-varying stroke.

B) Excluding first year of follow-up

	HZ				Comparison cohort				HR (95% CI)		
	No. of persons	No. of events	Person-years at risk	Rate per 1,000 person-years (95% CI)	No. of persons	No. of events	Person-years at risk	Rate per 1,000 person-years (95% CI)	Unadjusted[a]	Confounder-adjusted, model[b]	Mediation model[c]
All-cause dementia											
1–5 years	220654	3666	713061	5.14 (4.97–5.31)	1109520	21103	3549068	5.95 (5.87–6.03)	0.88 (0.85–0.91)	0.88 (0.85–0.91)	0.87 (0.84–0.91)
1–10 years	220654	6931	1230121	5.63 (5.50–5.77)	1109520	37926	6049723	6.27 (6.21–6.33)	0.90 (0.88–0.93)	0.90 (0.88–0.92)	0.90 (0.87–0.92)
1–15 years	220654	8760	1464143	5.98 (5.86–6.11)	1109520	46071	7147581	6.45 (6.39–6.50)	0.93 (0.91–0.95)	0.92 (0.90–0.95)	0.92 (0.90–0.95)
1–21 years	220654	9283	1532456	6.06 (5.93–6.18)	1109520	48602	7459618	6.52 (6.46–6.57)	0.93 (0.91–0.95)	0.93 (0.90–0.95)	0.92 (0.90–0.95)
Alzheimer's disease											
1–5 years	220654	1430	713061	2.01 (1.90–2.11)	1109520	8220	3549068	2.32 (2.27–2.37)	0.87 (0.82–0.92)	0.88 (0.83–0.93)	0.88 (0.83–0.93)
1–10 years	220654	2870	1230121	2.33 (2.25–2.42)	1109520	15451	6049723	2.55 (2.51–2.59)	0.90 (0.87–0.94)	0.91 (0.87–0.95)	0.91 (0.87–0.95)
1–15 years	220654	3706	1464143	2.53 (2.45–2.61)	1109520	19323	7147581	2.70 (2.67–2.74)	0.93 (0.89–0.96)	0.93 (0.90–0.97)	0.93 (0.90–0.97)
1–21 years	220654	3993	1532456	2.61 (2.52–2.69)	1109520	20632	7459618	2.77 (2.73–2.80)	0.93 (0.90–0.97)	0.93 (0.90–0.97)	0.93 (0.90–0.97)

Abbreviations: CI = confidence interval; HR = hazard ratio; HZ = herpes zoster
[a]Calculated with stratified Cox proportional hazards regression adjusted by design for birth and sex.
[b]Adjusted additionally for autoimmune disease, chronic kidney disease, chronic pulmonary disease, asthma, cancer, diabetes, glucocorticoids, human immunodeficiency virus, lipid-lowering therapy, and traumatic head injury.
[c]Adjusted additionally for time-varying stroke.

eTable 5. Number of events, accumulated person-time, rate, and hazard ratio (HRs) of dementia associated with a previous diagnosis of herpes zoster (HZ), Denmark, 1997–2017, sensitivity analyses.

	HZ				Comparison cohort				HR (95% CI)		
	No. of persons	**No. of events**	**Person-years at risk**	**Rate per 1,000 person-years (95% CI)**	**No. of persons**	**No. of events**	**Person-years at risk**	**Rate per 1,000 person-years (95% CI)**	**Unadjusted[a]**	**Confounder-adjusted, model[b]**	**Mediation model[c]**
0–1 years of follow-up											
Main analysis	247305	1238	233268	5.31 (5.01–5.60)	1235891	6332	1172114	5.40 (5.27–5.54)	0.99 (0.93–1.05)	0.98 (0.92–1.04)	0.98 (0.92–1.04)
HZ patients older than 60 years	149417	1224	139272	8.79 (8.30–9.28)	746495	6166	702108	8.78 (8.56–9.00)	1.00 (0.94–1.07)	1.00 (0.94–1.06)	1.00 (0.94–1.06)
HZ patients diagnosed before 2014 September (Zostavax)	194742	1068	189628	5.63 (5.29–5.97)	973379	5380	953464	5.64 (5.49–5.79)	1.00 (0.94–1.07)	0.99 (0.93–1.06)	0.99 (0.93–1.06)
Not censoring comparators at HZ diagnosis[d]	247305	1238	233269	5.31 (5.01–5.60)	1235891	6367	1176680	5.41 (5.28–5.54)	0.99 (0.93–1.05)	0.98 (0.92–1.04)	0.98 (0.92–1.04)
Excluding anti-dementia drugs from the outcome definition	247305	1161	233269	4.98 (4.69–5.26)	1235891	5925	1172114	5.05 (4.93–5.18)	0.99 (0.93–1.05)	0.98 (0.92–1.04)	0.98 (0.92–1.04)
Adjusting additionally for cardiovascular and liver diseases	247305	1238	233268	5.31 (5.01–5.60)	1235891	6332	1172114	5.40 (5.27–5.54)	0.99 (0.93–1.05)	0.98 (0.92–1.04)[d]	
1–21 years of follow-up											
Main analysis	220654	9283	1532456	6.06 (5.93–6.18)	1109520	48602	7459618	6.52 (6.46–6.57)	0.93 (0.91–0.95)	0.93 (0.90–0.95)	0.92 (0.90–0.95)
HZ patients older than 60 years	130418	8724	791099	11.03 (10.80–11.26)	658774	45857	3876787	11.83 (11.72–11.94)	0.93 (0.90–0.95)	0.92 (0.90–0.95)	0.92 (0.90–0.95)
HZ patients	185555	9108	1492972	6.10 (5.98–	933736	47616	7262948	6.56 (6.50–	0.93 (0.91–	0.93 (0.90–	0.93 (0.90–

diagnosed before 2014 September (Zostavax)				6.23)				6.61)	0.95)	0.95)	0.95)
Not censoring comparators at HZ diagnosis[d]	220654	9283	1532456	6.06 (5.93–6.18)	1118222	51429	7835599	6.56 (6.51–6.62)	0.94 (0.91–0.96)	0.93 (0.91–0.95)	0.93 (0.91–0.95)
Excluding anti-dementia drugs from the outcome definition	220654	8543	1532456	5.57 (5.46–5.69)	1109520	44851	7459618	6.01 (5.96–6.07)	0.93 (0.91–0.95)	0.92 (0.90–0.95)	0.93 (0.90–0.95)
Adjusting additionally for cardiovascular and liver diseases	220654	9283	1532456	6.06 (5.93–6.18)	1109520	48602	7459618	6.52 (6.46–6.57)	0.93 (0.91–0.95)	0.92 (0.90–0.95)[e]	

Abbreviations: CI = confidence interval; HR = hazard ratio; HZ = herpes zoster

[a]Calculated with stratified Cox proportional hazards regression adjusted by design for birth year and sex.

[b]Adjusted additionally for autoimmune disease, chronic kidney disease, chronic pulmonary disease, asthma, cancer, diabetes, glucocorticoids, human immunodeficiency virus, lipid-lowering therapy, and traumatic head injury.

[c]Adjusted additionally for time-varying stroke.

[d]Changing the censoring criteria so that people in the comparison cohort who joined the zoster exposed cohort during follow-up continued to be followed in the comparison cohort as well.

[e]Adjusted for autoimmune disease, chronic kidney disease, chronic pulmonary disease, asthma, cancer, diabetes, glucocorticoids, human immunodeficiency virus, lipid-lowering therapy, and traumatic head injury *as well as* acute myocardial infarction, angina pectoris, heart failure, hypertension and liver disease.

eTable 6. Number of events, accumulated person-time, rate, and hazard ratio (HRs) of Alzheimer's dementia associated with a previous diagnosis of herpes zoster (HZ), Denmark, 1997–2017, sensitivity and *post hoc* analyses.

	HZ				Comparison cohort				HR (95% CI)		
	No. of persons	**No. of events**	**Person-years at risk**	**Rate per 1,000 person-years (95% CI)**	**No. of persons**	**No. of events**	**Person-years at risk**	**Rate per 1,000 person-years (95% CI)**	**Unadjusted[a]**	**Confounder-adjusted, model[b]**	**Mediation model[c]**
0–1 years of follow-up											
Main analysis	247305	418	233269	1.79 (1.62–1.96)	1235891	2336	1172114	1.99 (1.91–2.07)	0.91 (0.82–1.01)	0.91 (0.82–1.01)	0.91 (0.82–1.01)
HZ patients older than 60 years	149417	416	139272	2.99 (2.70–3.27)	746495	2298	702108	3.27 (3.14–3.41)	0.92 (0.82–1.02)	0.92 (0.83–1.02)	0.92 (0.83–1.02)
HZ patients diagnosed before 2014 September (Zostavax)	194742	324	189629	1.71 (1.52–1.89)	973379	1827	953464	1.92 (1.83–2.00)	0.90 (0.80–1.01)	0.90 (0.80–1.01)	0.90 (0.80–1.01)
Not censoring comparators at HZ diagnosis[d]	247305	418	233269	1.79 (1.62–1.96)	1235891	2349	1176680	2.00 (1.92–2.08)	0.90 (0.81–1.00)	0.91 (0.82–1.01)	0.91 (0.82–1.01)
Excluding anti-dementia drugs from the outcome definition	247305	341	233269	1.46 (1.31–1.62)	1235891	1929	1172114	1.65 (1.57–1.72)	0.89 (0.80–1.00)	0.90 (0.80–1.01)	0.90 (0.80–1.01)
Adding unspecific codes for dementia for defining Alzheimer's disease	247305	535	233269	2.29 (2.10–2.49)	1235891	2787	1172114	2.38 (2.29–2.47)	0.97 (0.88–1.06)	0.97 (0.88–1.06)	0.97 (0.88–1.06)
After censoring people diagnosed with Lewy body dementia during follow-up	241791	385	227992	1.69 (1.52–1.86)	1213670	2188	1150607	1.90 (1.82–1.98)	0.89 (0.80–1.00)	0.90 (0.81–1.00)	0.90 (0.81–1.01)
Adjusting additionally for cardiovascular and	247305	418	233269	1.79 (1.62–1.96)	1235891	2336	1172114	1.99 (1.91–2.07)	0.91 (0.82–1.01)	0.91 (0.82–1.01)[e]	

liver diseases											
1–21 years of follow-up											
Main analysis	220654	3993	1532456	2.61 (2.52–2.69)	1109520	20632	7459618	2.77 (2.73–2.80)	0.93 (0.90–0.97)	0.93 (0.90–0.97)	0.93 (0.90–0.97)
HZ patients older than 60 years	130418	3773	791099	4.77 (4.62–4.92)	658774	19595	3876787	5.05 (4.98–5.13)	0.93 (0.89–0.96)	0.93 (0.90–0.97)	0.93 (0.90–0.97)
HZ patients diagnosed before 2014 September (Zostavax)	185555	3893	1492972	2.61 (2.53–2.69)	933736	20106	7262948	2.77 (2.73–2.81)	0.93 (0.90–0.97)	0.93 (0.90–0.97)	0.94 (0.90–0.97)
Not censoring comparators at HZ diagnosis[d]	220654	3993	1532456	2.61 (2.52–2.69)	1118222	21906	7835599	2.80 (2.76–2.83)	0.94 (0.90–0.97)	0.94 (0.91–0.98)	0.94 (0.91–0.98)
Excluding anti-dementia drugs from the outcome definition	220654	3253	1532456	2.12 (2.05–2.20)	1109520	16881	7459618	2.26 (2.23–2.30)	0.93 (0.89–0.97)	0.93 (0.89–0.97)	0.93 (0.89–0.97)
Adding unspecific codes for dementia for defining Alzheimer's disease	220654	4797	1532456	3.13 (3.04–3.22)	1109520	24407	7459618	3.27 (3.23–3.31)	0.95 (0.92–0.98)	0.95 (0.92–0.98)	0.95 (0.92–0.98)
After censoring people diagnosed with Lewy body dementia during follow-up	215618	3660	1486912	2.46 (2.38–2.54)	1088765	19099	7288302	2.62 (2.58–2.66)	0.93 (0.89–0.96)	0.93 (0.90–0.97)	0.93 (0.90–0.97)
Adjusting additionally for cardiovascular and liver diseases	220654	3993	1532456	2.61 (2.52–2.69)	1109520	20632	7459618	2.77 (2.73–2.80)	0.93 (0.90–0.97)	0.94 (0.90–0.97)[e]	

Abbreviations: CI = confidence interval; HR = hazard ratio; HZ = herpes zoster

[a]Calculated with stratified Cox proportional hazards regression adjusted by design for birth year and sex.

[b]Adjusted additionally for autoimmune disease, chronic kidney disease, chronic pulmonary disease, asthma, cancer, diabetes, glucocorticoids, human immunodeficiency virus, lipid-lowering therapy, and traumatic head injury.

[c]Adjusted additionally for time-varying stroke.

[d]Changing the censoring criteria so that people in the comparison cohort who joined the zoster exposed cohort during follow-up continued to be followed in the comparison cohort as well.

[e]Adjusted for autoimmune disease, chronic kidney disease, chronic pulmonary disease, asthma, cancer, diabetes, glucocorticoids, human immunodeficiency virus, lipid-lowering therapy, and traumatic head injury *as well as* acute myocardial infarction, angina pectoris, heart failure, hypertension and liver disease.