Accepted Manuscript

British Journal of General Practice

The Association between Vitamin D and Incident Herpes Zoster: A UK Biobank Study

Lin, Liang-Yu; Mathur, Rohini; Mulick, Amy ; Smeeth, Liam; Langan, Sinéad; Warren-Gash, Charlotte

DOI: https://doi.org/10.3399/BJGP.2021.0623

To access the most recent version of this article, please click the DOI URL in the line above.

Received 02-November-2021
Revised 16-February-2022
Accepted 30-March-2022

Title: The Association between Vitamin D and Incident Herpes Zoster: A UK Biobank Study

List title: Vitamin D and Herpes Zoster

Authors:

Liang-Yu Lin[1], MD MSc, PhD student,

ORCID: https://orcid.org/0000-0003-4720-6738

Rohini Mathur[1], BSc MSc PhD, Associate Professor,

ORCID: https://orcid.org/0000-0002-3817-8790

Amy Mulick[1], BSc MA MSc, Research Fellow,

ORCID: https://orcid.org/0000-0002-4009-2080

Liam Smeeth[1], MBChB FRCGP FFPH FRCP MSc PhD FMedSci, Professor,

ORCID: https://orcid.org/0000-0002-9168-6022

Sinéad M Langan[1*], FRCP MSc PhD, Professor,

ORCID: https://orcid.org/0000-0002-7022-7441

Charlotte Warren-Gash[1*], FFPH FRCP Edin PhD, Associate Professor,

ORCID: https://orcid.org/0000-0003-4524-3180

* Joint senior authors

Authors' affiliations:

1. Faculty of Epidemiology & Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK WC1E 7HT

Corresponding to

Liang-Yu Lin (liang-yu.lin@lshtm.ac.uk)

Data sharing statement:

Other researchers can apply for UK Biobank data to answer specific research questions. We have uploaded our analysis codes to GitHub (https://github.com/liang-yu12/ukb_vd_hz_publish)

Abstract

Background:

Although vitamin D has immunomodulatory effects, any association with herpes zoster (HZ) is unclear.

Aim:

To explore the association between vitamin D status and the risk of incident HZ in adults in the UK.

Design and setting:

We conducted a cohort study including participants from UK Biobank, who had at least one vitamin D testing result with linked primary care electronic health records.

Methods:

The primary exposure was vitamin D status, categorised as deficient (< 25 nmol/L), insufficient (25–50 nmol/L) or sufficient (≥ 50 nmol/L). The secondary exposures were self-reported vitamin D supplementation at baseline assessment and vitamin D prescription records. The outcome was diagnosed incident HZ, identified from linked primary care or hospital inpatient records. We used Weibull regression, adjusting for potential confounders including demographic factors, comorbidities and immunosuppression.

Results:

We included 177,572 eligible participants in our analysis with mean follow-up time of 10.1 (SD=1.9) years. No evidence showed that low vitamin D was associated with a higher incidence of HZ, compared with people with sufficient vitamin D (deficient: adjusted hazard ratio [HR] = 0.99, 95% confidence interval [CI] = 0.90–1.10; insufficiency: RR = 1.03, CI = 0.96–1.10.) We found no evidence that vitamin D supplementations or receiving vitamin D prescription was associated with HZ incidence (supplementation: HR = 0.88, CI = 0.67–1.16; prescription: HR = 1.11, CI = 0.91–1.34.)

Conclusion:

We observed no association of vitamin D status, supplementation or prescription with incident HZ. No evidence supported vitamin D supplementation as a strategy to prevent HZ.

Keywords:

Vitamin D, Herpes zoster, Electronic Health Records, primary health care, UK Biobank

(Abstract word count: 249/250 words)

How this fits in:

Vitamin D is regarded as having some antimicrobial effects. We used large nationwide cohort data to explore the association between vitamin D status and the risk of herpes zoster. Our results showed that neither serum vitamin D status, vitamin

D supplementation, nor vitamin D prescriptions in primary care was associated with incident herpes zoster. Based on currently available evidence, vitamin D supplements are not an effective intervention to prevent herpes zoster.

Introduction

Herpes zoster is a common disease among adults. In the UK, its annual incidence is around 5 per 1,000 person-years, and its average lifetime risk is around 30% in people without vaccination (1, 2). The typical symptoms are unilateral painful vesicular rashes in a dermatomal distribution, lasting about seven to ten days. Herpes zoster significantly decreases patients' quality of life and substantially increases medical and social costs (1). It may also be associated with a range of neurological, ocular, cutaneous and visceral complications (3). The most important risk factor for herpes zoster is ageing because immunity wanes over time (4). Immunosuppression and some comorbidities such as chronic kidney disease (CKD), and systematic lupus erythematosus (SLE) are also associated with increased herpes zoster risk (5). Vaccines are effective for reducing the risk of herpes zoster (6). However, in the UK, the vaccination programme is only available for people aged 70 years or greater (7). Studying other possible preventive measures for herpes zoster is important, especially for people under the age of 70.

The musculoskeletal protection effects of vitamin D have been well-established because it regulates calcium and phosphate homeostasis (8). In addition, the non-skeletal effects of vitamin D have been recently studied, such as immunomodulation. In vitro studies have shown that vitamin D could stimulate the expression of antimicrobial peptides, protecting against infections (9, 10). However, epidemiological

studies have shown inconsistent associations between vitamin D and infections. A systematic review and meta-analysis published in 2021, combining 37 clinical trials of vitamin D supplementation, showed that taking vitamin D slightly decreased the risk of respiratory infections (odds ratio = 0.92, 95% CI = 0.86–0.99) (11). Our previous systematic review and meta-analysis found inconclusive evidence for any association between vitamin D and herpesviruses in studies conducted primarily among immunosuppressed individuals (12). One case-control study among people with CKD showed that vitamin D supplementation may decrease the odds of herpes zoster (13).

If vitamin D deficiency is associated with an increased risk of herpes zoster in the general population, taking vitamin D supplements may become a cheap public health measure for its prevention. Therefore, we aimed to explore the association between serum vitamin D status or supplementation and the risk of herpes zoster using the UK Biobank cohort.

Methods

Data source

Our data source was UK Biobank, a nationwide cohort recruited between 2006 and 2010, consisting of approximately half a million participants aged 40 to 69 years from England, Wales and Scotland. At recruitment, participants visited 22 UK Biobank assessment centres, in which they received physical examinations, completed questionnaires and gave biological samples including blood, urine and saliva (14). Participants also consented to have their clinical data linked, including diagnosis codes for inpatient and outpatient visits, the dates of diagnosis, the dates of each hospitalisation episode or consultation, and prescribing records from primary care

(15, 16). Nearly all participants have linked hospital inpatient records, and around 230,000 participants also have their primary care records linked (17).

Primary exposure: vitamin D status

The primary exposure of our study was serum vitamin D status recorded between 2006 and 2010. The detailed methods for measurement of serum vitamin D levels are described in the **Supplementary Box 1**. Participants' with serum 25-hydroxyvitamin D levels less than 25 nmol/L were coded as deficient, between 25 and 50 nmol/L as insufficient, and greater than or equal to 50 nmol/L as sufficient following Public Health England's definition (18).

Secondary exposure: vitamin D supplementation

A secondary exposure, vitamin D supplementation, was recorded using a self-reported questionnaire during participants' baseline visits between 2006 and 2010. This included self-reported use of over-the-counter supplements, such as vitamin D, multivitamins, fish oil and calcium. Another secondary exposure was general practitioner (GP)-prescribed vitamin D supplementation, obtained from the GP prescription data within two years before the baseline assessment. The detailed data management of secondary exposures is summarised in the **Supplementary Box 2**.

Outcome

The outcome of our study was incident herpes zoster, defined through clinical diagnosis recorded in the linked primary care and inpatient records. We developed diagnosis code-lists for herpes zoster in Read 2, Clinical Terms Version 3 (CTV3), and International Classification of Diseases version 10 (ICD-10) codes to identify incident herpes zoster from the dataset (15, 16). Incident herpes zoster diagnoses were defined as participants with a herpes zoster diagnosis occurring at least one

day after the start of follow-up from the baseline assessment to 31 July 2019 (**Figure 1**).

Study eligibility

The study design is summarised in **Figure 1**. UK Biobank participants were eligible if they had at least one vitamin D record, with both primary care and inpatient care records. Participants with no vitamin D record, with no linked electronic health records (EHR) or with previous herpes zoster or post-herpetic neuralgia within five years before follow-up were excluded (**Figure 1**).

Measurement of covariates

Some demographic factors associated with vitamin D deficiency and insufficiency were recorded at baseline assessment, including sex, age, ethnicity, body mass index (BMI), smoking status, drinking frequency, Index of Multiple Deprivation (IMD), regions of UK Biobank assessment centres and the seasons when vitamin D was tested (19). We also identified comorbidities associated with an increased risk of herpes zoster, such as CKD and SLE, from the linked EHR and self-reported health conditions (5). Severe immunosuppressive conditions, including organ transplantation, chemoradiotherapy, cell-mediated immunosuppression, HIV, blood cancers, chemotherapy (biological and non-biological agents), bone marrow transplantation and long-term oral steroid use were identified solely from the clinical datasets. Long-term oral steroid use was defined as at least two steroid prescriptions within 90 days. We defined these clinical covariates as ever had a diagnostic code within five years before the follow-up. For blood cancer, bone marrow transplantation and steroid use, the covariate assessment time windows were up to two years before follow-up (**Figure 1**.)

Statistical analysis

This was a historical cohort study. We followed participants from the date when they visited the assessment centre. The end of follow-up was defined as the date that herpes zoster was diagnosed, the date of death or loss to follow-up, or 31 July 2019, whichever was first. The demographic characteristics of the included participants were compared by their vitamin D status, and the included and excluded participants were further compared. We assessed the association between the primary and secondary exposures and incident herpes zoster using Weibull regression models, adjusting for possible confounders selected by using a directed acyclic graph approach, summarised in **Supplementary Figure S1**. Our models included sex, age, BMI, ethnicity, smoking status, drinking frequency, IMD scores, regions of UK Biobank assessment centres, vitamin D testing seasons, underlying comorbidities and immunosuppression, which are described in the **Supplementary Box 3**. The number of participants with missing data was less than 3% across demographic and health-related factors, with the exception of self-reported vitamin D supplementation, which had 54.5% missing data. Because the proportion of missingness in most demographic factors was low, and the chance of being a complete case was not dependent on our outcome, we performed a complete case analysis only including people without missing data in our models (20). All statistical analysis and plotting were performed using R Statistical Software (version 4.1.1, R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analysis

We performed various sensitivity analyses, and the justification is summarised in **Table 1**. We excluded records after September 2013, following the introduction of the vaccination program, and we compared the effects of different covariate definitions.

To eliminate the potential effect of time-varying hazards, we also reran analyses using the Cox proportional-hazards regression model. We also used Poisson regression assuming baseline hazards is constant (**Table 1**).

Results

Study population

The selection of the study population is summarised in **Figure 2**. After excluding people without vitamin D records, without clinical records, or with previous herpes zoster episodes, we included 177,572 participants in our analysis. Among these included participants, 6,583 (3.7%) people died, 211 lost to follow-up (0.12%), and 6,616 (3.7%) participants had incident HZ diagnosis. Among people with outcomes, more people had sufficient vitamin D levels (N=2,948, 45%), compared with people with insufficient (N=2,806, 42%) or deficient (N=862, 13%) vitamin D. A comparison of the included and excluded participants is summarised in **Supplementary Table S1**. The distribution of demographic factors was similar between the included and excluded participants, and more people from Yorkshire and the Humber, Scotland and East Midlands area were included in our analysis. The proportion of missingness across demographic factors was below 3%, and 54.5% of self-reported vitamin D supplementations were missing (**Supplementary Table S2**).

The distribution of demographic factors by vitamin D status is summarised in **Supplementary Table S3**. Across different vitamin D statuses, the distributions of sex, age, comorbidities and immunosuppression were similar. More participants with Asian or Black ethnic backgrounds were vitamin D deficient at baseline. Participants in the vitamin D deficient group were more likely to be obese, smoked more and lived in more deprived areas, and they drank less frequently and were less likely to receive vitamin D prescriptions. More people with vitamin D deficiency were tested during winter, and more vitamin D deficient participants were from Scotland than from other

countries. The mean follow-up periods of people with different vitamin D statuses were similar, with an average of 10 years (**Supplementary Table S3**).

Association between vitamin D and risk of herpes zoster

The associations between vitamin D status and the risk of incident herpes zoster are summarised in **Figure 3**. Compared with people with sufficient vitamin D status, some evidence existed that vitamin D deficiency was associated with a decreased risk of incident herpes zoster in the crude Weibull regression model (hazard ratio [HR] = 0.86, 95% confidence interval [CI] = 0.79–0.95). However, in models adjusted for sex and age, as well as models fully adjusted for all covariates, no evidence showed that vitamin D deficiency or insufficiency were associated with incident herpes zoster (partially adjusted model: insufficiency HR = 1.01, CI = 0.95–1.08; deficient HR = 0.96, CI = 0.87–1.05; fully adjusted model: insufficiency HR = 1.03, CI = 0.90–1.10; deficient HR = 0.99, CI = 0.90–1.10; **Figure 3).**

Association between vitamin D supplementation and risk of incident herpes zoster

Figure 4a shows the association between self-reported vitamin D supplementation and the risk of incident herpes zoster. We found no evidence that self-reported vitamin D supplement use was associated with incident herpes zoster in the subgroup of participants for whom this information was recorded. Some evidence existed that ever having received vitamin D prescriptions was associated with an increased risk of herpes zoster in the crude (HR = 1.59, 95% CI= 1.33–1.91) and partially adjusted models (HR = 1.27, 95% CI= 1.06–1.52). However, such association disappeared after fully adjusting for potential confounders (HR = 1.11, 95% CI = 0.91–1.34) (**Figure 4b**).

Sensitivity analyses

After excluding records after 1 September 2013, the main findings remained similar. Neither vitamin D deficiency nor insufficiency (**Supplementary Figure S2**), nor vitamin D supplementation (**Supplementary Figure S3a)**, nor receiving vitamin D prescription (**Supplementary Figure S3b**) provided evidence of an association with herpes zoster. We compared different covariate definitions, and the results did not differ from the initial model (**Supplementary Figure S4**). The stratified Cox regression model showed no evidence of an association between vitamin D status and incident herpes zoster, either before or after the vaccination program was initiated (**Supplementary Figure S5**). The Cox proportional-hazards model showed no evidence of an association between vitamin D supplementation and herpes zoster (**Supplementary Figure S6a**), whereas weak evidence existed that vitamin D prescription was associated with a higher risk of herpes zoster (adjusted HR = 1.17, 95%CI=1.00-1.37, **Supplementary Figure S6b.**) The Poisson regression model showed no evidence of an association of vitamin D status, supplementation or prescription with herpes zoster (**Supplementary Figure S7** and **Supplementary Figure S8.**)

Discussion

Summary

We found no evidence of an association between vitamin D deficiency or insufficiency and incident herpes zoster after adjusting for potential confounders. Self-reported vitamin D supplementation or receiving vitamin D prescriptions showed no evidence of an association with incident herpes zoster. The results were robust across a range of sensitivity analyses such as excluding records during the shingles vaccination period and adjusting for differing definitions of confounding factors.

Strengths and limitations

Our study has several strengths. First, compared to previous small studies conducted with clinically high-risk individuals, our large study of a general population provides greater statistical power and generalisability. Second, the vitamin D levels were measured systematically, and the proportion of missingness of covariates was relatively low. Third, the linkage between UK Biobank and the primary and secondary care records enabled us to follow up with participants for a long time and identify incident cases.

Nevertheless, some limitations of our study also need to be stressed. First, the exposure and some covariates are probably time-dependent, but we used the measures taken at baseline. In our previous analysis, the proportion of vitamin D deficiency was lowest in summer, and it was more prevalent in winter and spring (19). In another study measuring vitamin D repeatedly, the intraclass correlation coefficient between two vitamin D measurements after five years was only 0.59, which was moderately reliable (21). In our analysis, we used Weibull regression which assumes hazards increase during follow-up, and we adjusted for vitamin D

testing seasons in our model to minimise the effect of seasonal variation. In sensitivity analysis, we used the Cox model regression to adjust for potentially time-varying hazards, and the results remained similar. Second, despite the completeness of most covariates, for self-reported vitamin D supplementation, more than half of the data were missing. Therefore, this variable may not reflect the real vitamin D supplementation use, and its association with the outcome needs to be interpreted carefully.

Third, the outcomes might be under-ascertained. We defined herpes zoster using EHR, but people with more comorbidities may visit their primary care physicians more frequently. Thus, herpes zoster among these people is more likely to be diagnosed, while mild shingles among a younger or healthier population might not be noticed (22). In our study population, although the proportions of people with diabetes and chronic obstructive pulmonary disease were slightly higher in the vitamin D deficiency group, the overall distributions of comorbidities and immunosuppression were similar across different vitamin D statuses. Any ascertainment bias in our study should be non-differential.

Fourth, misclassification of HZ outcomes cannot be ruled out. Studies using EHR assume that individuals have a disease if they have the corresponding diagnostic codes. Conversely, people without specific diagnostic codes are assumed not to have a disease. It is possible that some participants with HZ did not visit their GP or did not have a confirmed diagnosis, so their disease statuses may remain unrecorded. Regarding possible ascertainment bias, a study in the US reported that using the ICD-10 code for HZ (code 053) could identify 98% of herpes zoster cases (sensitivity = 98%), and the positive predictive value was also very high (PPV = 93%) (23). Furthermore, the financial barrier to access to healthcare in the UK is generally

lower than in the US, which may increase the sensitivity of HZ diagnoses in the EHR databases.

Lastly, residual confounding effects cannot be ruled out. Using diagnostic codes from the linked records may underestimate the true prevalence of some diseases, such as CKD. In studies using EHR, serum creatinine levels are more often used to diagnose CKD (24). However, laboratory test results are not available in the linked EHR of UK Biobank. To enhance the sensitivity of detecting comorbidities, we included self-reported non-cancer health conditions in our analysis, but the overall prevalence of CKD was still much lower than the national prevalence during the same period (25).

Comparison with existing literature

Ours is the first published study assessing the association between vitamin D status and incident herpes zoster in the general population. Previous studies on this topic have been conducted among people with immunosuppression. For instance, a small case-control study among CKD patients showed that patients taking vitamin D supplements had lower odds of having herpes zoster (13). Compared to previous studies, our study population was largely immunocompetent.

We found no evidence of an association between self-reported or prescribed vitamin D supplements and incident herpes zoster, although the great proportion of missing data in self-reported vitamin D supplements may have biased the results. A positive trend of association between GP-prescribed vitamin D supplementation and herpes zoster was noted in the crude, partially adjusted model and in the sensitivity analysis. This association may be due to confounding by indication, as well as the underestimation of unreported food fortification. People receive vitamin D prescriptions to prevent or treat vitamin D deficiency, but we did not consider the indication for the prescription. Vitamin D food fortification is another main source of

vitamin D supplementation in the UK primary care setting (26). However, due to the limitation of data availability, this was not included in our analysis.

Implications for research and/or practice

Our cohort study showed no evidence to support an association between vitamin D status or supplementation and incident herpes zoster. Based on currently available evidence, vitamin D testing, supplementation or fortification cannot be recommended to prevent herpes zoster.

Funding statement:

LYL is funded by the scholarship of government sponsorship for overseas study by the Ministry of Education Republic of China (Taiwan). RM is funded by a Sir Henry Wellcome Postdoctoral Fellowship (201375/Z/16/Z). CWG is supported by a Wellcome Intermediate Clinical Fellowship. SML is funded by a Wellcome Senior Clinical Fellowship in Science. This research was funded in whole or in part by the Wellcome Trust [grant number: 201375/Z/16/Z, 201440/Z/16/Z, 205039/Z/16/Z]. For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript (AAM) version arising from this submission.

Ethical approval

The UK Biobank project was approved by the Northwest Haydock Research Ethics Committee (reference: 11/NW/0382). Our project was approved by UK Biobank

(ID:51265) and the Research Ethics Committee of the London School of Hygiene and Tropical Medicine (reference: 17158).

Competing interests

Professor Liam Smeeth is an expert that has been consulted by UK Biobank for biomarkers to be included. All authors declare that they have no known conflicts of interest.

Acknowledgements

We thank Ms Rutendo Muzambi for assistance with data management of prescription data.

References

1. Gauthier A, Breuer J, Carrington D, et al. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect. 2009;137(1):38-47.
2. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect. 2001;127(2):305-14.
3. Forbes HJ, Bhaskaran K, Grint D, et al. Incidence of acute complications of herpes zoster among immunocompetent adults in England: a matched cohort study using routine health data*. Br J Dermatol. 2021;184(6):1077-84.
4. Cohen JI. Clinical practice: Herpes zoster. New England Journal of Medicine. 2013;369(3):255-63.
5. Forbes HJ, Bhaskaran K, Thomas SL, et al. Quantification of risk factors for herpes zoster: population based case-control study. BMJ. 2014;348:g2911.
6. Amirthalingam G, Andrews N, Keel P, et al. Evaluation of the effect of the herpes zoster vaccination programme 3 years after its introduction in England: a population-based study. The Lancet Public Health. 2017;2667:1-9.
7. Public Health England. Shingles: guidance and vaccination programme 2013 [updated 13 March 2020. Available from: https://www.gov.uk/government/collections/shingles-vaccination-programme.
8. Holick MF. Vitamin D deficiency. New England Journal of Medicine. 2007;357(3):266-81.

9. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006;311(5768):1770-3.
10. Weber G, Heilborn JD, Chamorro Jimenez CI, et al. Vitamin D induces the antimicrobial protein hCAP18 in human skin. J Invest Dermatol. 2005;124(5):1080-2.
11. Jolliffe DA, Camargo CA, Jr., Sluyter JD, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. Lancet Diabetes Endocrinol. 2021.
12. Lin L-Y, Bhate K, Forbes H, et al. Vitamin D Deficiency or Supplementation and the Risk of Human Herpesvirus Infections or Reactivation: A Systematic Review and Meta-analysis. Open Forum Infect Dis. 2020;8(1).
13. Chao CT, Lai CF, Huang JW. Risk factors for herpes zoster reactivation in maintenance hemodialysis patients. Eur J Intern Med. 2012;23(8):711-5.
14. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.
15. UK Biobank. Primary Care Linked Data 2019 [Available from: https://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=591.
16. UK Biobank. Hospital inpatient data 2020 [updated August 2020. 3.0:[Available from: https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=138483.
17. UK Biobank. Health-related outcomes data 2021 [updated April 1st 2021. Available from: https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/health-related-outcomes-data.
18. The Scientific Advisory Committee on Nutrition. Vitamin D and Health. London: Public Health England 2016 21 July 2016.
19. Lin L-Y, Smeeth L, Langan S, et al. Distribution of vitamin D status in the UK: a cross-sectional analysis of UK Biobank. BMJ Open. 2021;11(1):e038503.
20. Hughes RA, Heron J, Sterne JAC, et al. Accounting for missing data in statistical analyses: multiple imputation is not always the answer. Int J Epidemiol. 2019;48(4):1294-304.
21. Meng JE, Hovey KM, Wactawski-Wende J, et al. Intraindividual variation in plasma 25-hydroxyvitamin D measures 5 years apart among postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2012;21(6):916-24.
22. Batram M, Witte J, Schwarz M, et al. Burden of Herpes Zoster in Adult Patients with Underlying Conditions: Analysis of German Claims Data, 2007-2018. Dermatol Ther (Heidelb). 2021;11(3):1009-26.
23. Klompas M, Kulldorff M, Vilk Y, et al. Herpes zoster and postherpetic neuralgia surveillance using structured electronic data. Mayo Clin Proc. 2011;86(12):1146-53.
24. McDonald HI, Shaw C, Thomas SL, et al. Methodological challenges when carrying out research on CKD and AKI using routine electronic health records. Kidney Int. 2016;90(5):943-9.
25. Public Health England. Chronic kidney disease (CKD) prevalence model: Public Health England,; 2014 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/612303/ChronickidneydiseaseCKDprevalencemodelbriefing.pdf.
26. Wan M, Patel A, Patel JP, et al. Quality and use of unlicensed vitamin D preparations in primary care in England: Retrospective review of national prescription data and laboratory analysis. Br J Clin Pharmacol. 2021;87(3):1338-46.

Figure 1. Study design diagram

Figure 2. The diagram of selecting eligible participants

Figure 3. The association between vitamin D status and the risk of herpes zoster. Crude: simple Weibull regression model without adjustment; Partially adjusted: Weibull regression model adjusted for sex and age; Fully adjusted: multivariable Weibull regression model adjusted for covariates, including sex, age, ethnicity, body mass index (BMI), smoking status, drinking frequency, Index of multiple deprivation (IMD), regions, seasons, comorbidities, and immunosuppressive conditions.

Figure 4 a. The association between self-reported vitamin D supplementation and the risk of herpes zoster; **b.** the association between receiving vitamin D prescriptions and the risk of herpes zoster. Model explanation: Crude: simple Weibull regression model without adjustment; Partially adjusted: Weibull regression model adjusted for sex and age; Fully adjusted: multivariable Weibull regression model adjusted for all covariates including sex, age, ethnicity, BMI, smoking status, drinking frequency, IMD, regions, seasons, comorbidities, and immunosuppressive conditions.

Table 1. Sensitivity Analysis

Sensitivity analysis		Justification	Outcome figures
Model 1	Stop follow-up by 31 August 2013	In the UK, a universal herpes zoster vaccination program has initiated since September 2013 (1). Therefore, sensitivity model 1 used Weibull regression excluding records after September 2013 to minimize the interference of vaccination.	Figure S2 Figure S3
Model 2	Comorbidities were only identified from clinical records	Self-reported non-cancer health conditions may not be accurate for identifying comorbidities. In sensitivity model 2 of Weibull regression, we defined comorbidities by using linked clinical records.	Figure S4
Model 3	In the immunosuppressive conditions, steroid use was defined as high dose steroid use	In sensitivity model 3, we defined immunosuppressive people with long term steroid use as those taking steroids greater or equal to 20 mg per day in the Weibull regression model.	Figure S4
Model 4	Comorbidities: exclude self-reported health conditions Immunosuppressive conditions: in steroid use, only include high dose users	Sensitivity model 4 used the covariates definition from both model 2 and model 3, to assess the effects of different covariates definitions in the Weibull regression model.	Figure S4
Model 5	Use Cox-regression to analyze the association between exposure and outcomes	Because some covariates are time-dependent, in sensitivity model 5 we used the cox regression model with the time scale of age. If the model violated the proportional hazard assumption, we would stratify the follow-up time on 1 September 2013, which was the date that the vaccination program initiated.	Figure S5 Figure S6
Model 6	Use Poisson regression to analyze the association between exposure and outcomes	We assumed the hazard of herpes zoster remains constant over follow-up, so in sensitivity model 6 we used the Poisson regression model to examine our hypothesis.	Figure S7 Figure S8

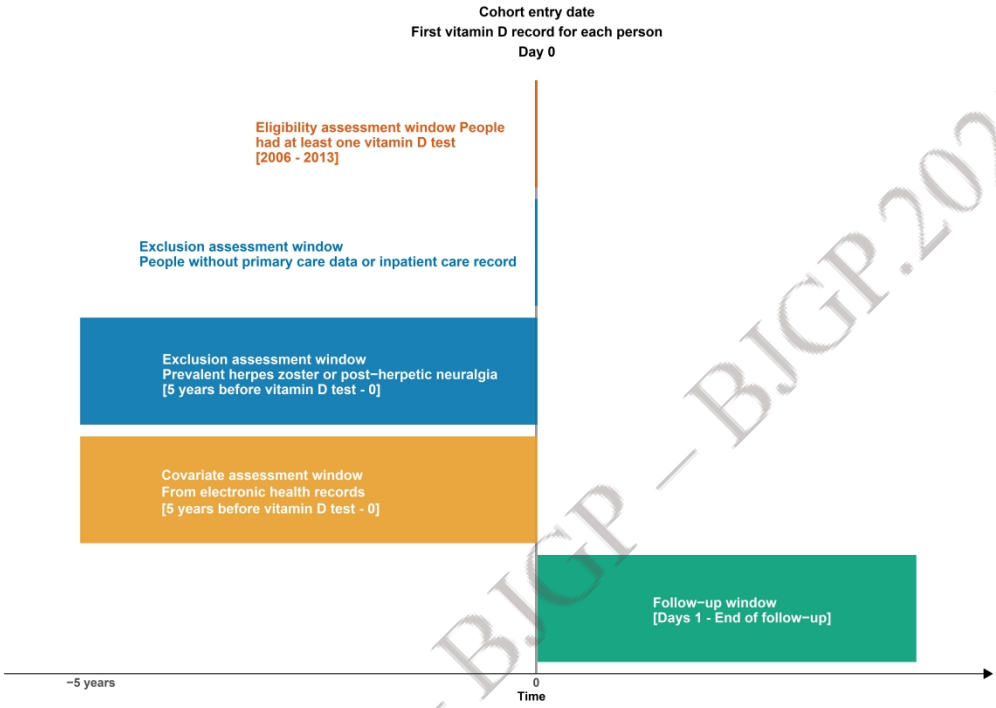

Figure 1. Study design diagram

406x304mm (400 x 400 DPI)

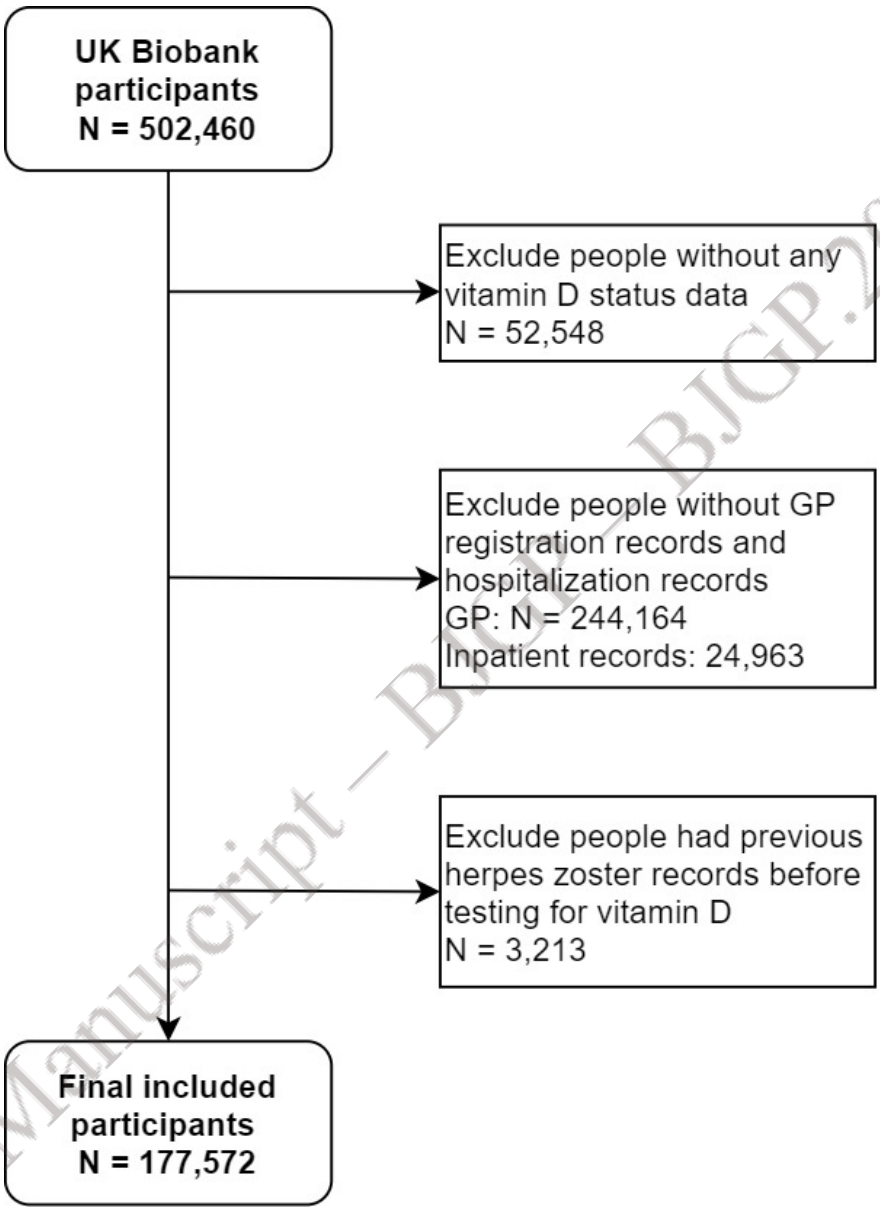

Figure 2. The diagram of selecting eligible participants

212x291mm (72 x 72 DPI)

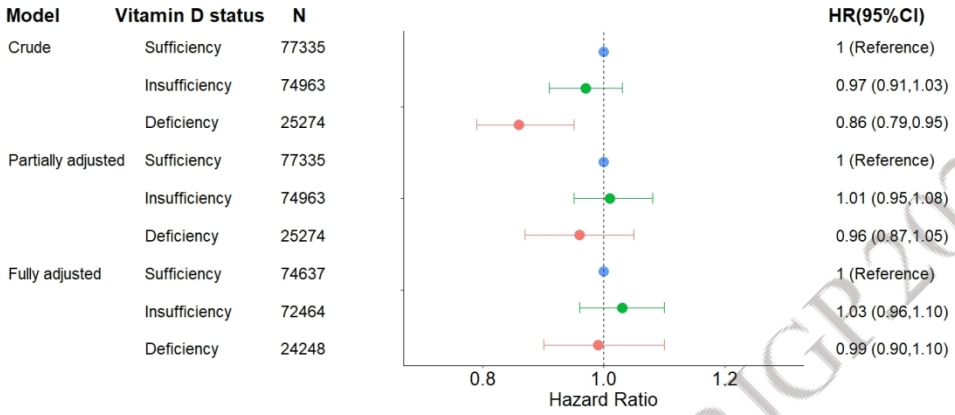

Figure 3. The association between vitamin D status and the risk of herpes zoster. Crude: simple Weibull regression model without adjustment; Partially adjusted: Weibull regression model adjusted for sex and age; Fully adjusted: multivariable Weibull regression model adjusted for covariates, including sex, age, ethnicity, body mass index (BMI), smoking status, drinking frequency, Index of multiple deprivation (IMD), regions, seasons, comorbidities, and immunosuppressive conditions.

383x158mm (96 x 96 DPI)

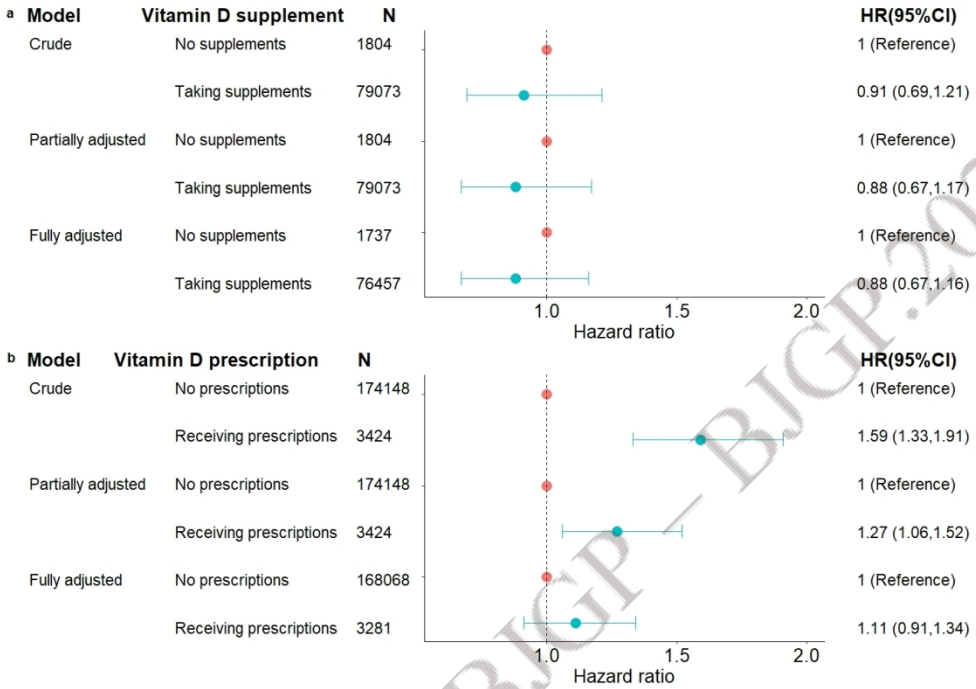

Figure 4 a. The association between self-reported vitamin D supplementation and the risk of herpes zoster; b. the association between receiving vitamin D prescriptions and the risk of herpes zoster. Model explanation: Crude: simple Weibull regression model without adjustment; Partially adjusted: Weibull regression model adjusted for sex and age; Fully adjusted: multivariable Weibull regression model adjusted for all covariates including sex, age, ethnicity, BMI, smoking status, drinking frequency, IMD, regions, seasons, comorbidities, and immunosuppressive conditions.

383x264mm (96 x 96 DPI)