BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers’ comments and the authors’ responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open’s open peer review process please email info.bmjopen@bmj.com
Association between statins use and herpes zoster

Journal: BMJ Open
Manuscript ID: bmjopen-2018-022897
Article Type: Research
Date Submitted by the Author: 13-Mar-2018
Complete List of Authors: guan, qiang; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Cardiology
fan, lai; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, urology
Wang, Yang-Yang; Wenzhou Medical University Second Affiliated Hospital, rehabilitation
liu, xiang; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, urology

Keywords: herpes zoster, statins, meta-analysis
Association between statins use and herpes zoster

Xueqiang Guan MD\textsuperscript{1}, Lailai Fan MD\textsuperscript{2}, Yangyang Wang MD\textsuperscript{3}, Xiang Liu MD\textsuperscript{2}

1. Department of Cardiology, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, Xueyuanxi Road, No. 109, Wenzhou, Zhejiang 325000, China
2. Department of urology, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University
3. Department of rehabilitation, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University

Correspondence should be addressed to Xueqiang Guan; wzsgxq@163.com

Funding source: None.

Data sharing statement: All relevant study data can be found in the online supplementary files.

Acknowledgements: We acknowledge that the Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University for supporting the work of our study.

Competing Interests: None.
Abstract

Objective-There is an increasing prevalence of cardiovascular disease, and the use of statins is increasing. Although statins are very effective lipid-lowering medications, they also have side effects. Recent evidence suggests that statins may increase the risk of herpes zoster.

Design-We performed a meta-analysis of observational studies to assess the association between statins use and the risk of herpes zoster infection. We searched PubMed and EMBASE for studies published from 1980 to 2017. Multivariate-adjusted odds ratios (ORs) were pooled using random-effect models, meta regression, subgroup and sensitivity analyses were performed to examine the source of heterogeneity.

Result-Five studies included nearly two million participants. The adjusted OR (95% confidence interval [CI]) related to herpes zoster was determined as 1.17 (95% CI: 1.10-1.24) among statins users.

Conclusion-The finding indicates that using statins may increase the risk of herpes zoster infection, although the number of included studies is limited and further studies are warranted.
Strengths and limitations of this study

1. This is the first systematic review and meta-analysis that specifically evaluated the association between statins use and the risk of herpes zoster.

2. The studies included in our meta-analysis included many participants and had a long-term follow-up time, which improves the statistical power of the meta-analysis.

3. This was a meta-analysis of observational studies so we could at best demonstrate an association but not a causal relationship.

4. We found a significant heterogeneity across studies, which might arise from regional differences, differences in the number of study participants and follow-up time. Additionally, the study by Chung et al. contributed much heterogeneity to the result.

5. We did not study the effects of different statins on risk of herpes zoster because of insufficient data. And the summary results might be influenced by the conversion of other measures to OR.
1. Introduction

Statins (3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors) are widely used to lower low-density lipoprotein cholesterol. Statins can reduce cardiovascular disease mortality and morbidity in patients with or without coronary heart disease\(^1\). Although statins are generally well tolerated, there are possible side effects that may affect skeletal muscle, cause diabetes mellitus, and decrease cognition, but these side effects are rare in clinical work, and their exact mechanisms are unclear\(^3\)\(^-\)\(^5\).

Herpes zoster causes dramatically suffering due to post-herpetic neuralgia or acute and chronic pain. The pain caused by inflammation and neuronal destruction disturbs the activities of daily life and decreases quality of life for the elderly\(^6\). Increasing age is the major risk factor for herpes zoster, and the risk is higher for women\(^7\). In Europe and the United States, the overall incidence of herpes zoster is three in one thousand, but increases sharply after sixty years old to ten in one thousand\(^8\). Vaccination can reduce the incidence rate of herpes zoster and post-herpetic neuralgia, and ease the burden of sickness associated with herpes zoster\(^9\).

Many epidemiologic studies reported the association between statins use and the risk of herpes zoster\(^10\)-\(^13\), but there was no meta-analysis providing an overview on this topic. Therefore, we conducted a comprehensive systematic review and meta-analysis of observational studies to assess the association between statins use and the risk of herpes zoster.

2. Methods

2.1 Search strategy
We followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) Guidelines\textsuperscript{14}. We first searched PubMed and EMBASE on December 20, 2015 for studies describing the association between statins and herpes zoster. To ensure our study was based on up-to-date results, we repeated the literature search of PubMed and EMBASE on October 30, 2017. We also checked the references of included studies and reviews. The search focused on two themes of subject terms and keywords: statins and herpes zoster. The detailed search strategies are presented in the supplemental material 1.

2.2 Study selection
Two investigators independently assessed literature eligibility, and disagreements were settled by discussion and consensus. Articles were included in the systematic review if: (1) the authors reported data from an original, peer-reviewed study (i.e., not review articles, or conference abstracts); (2) the study was a cohort study or case-control study, case report was not included due to lower quality of evidence-based medical evidence; and (3) the authors reported risk estimates of herpes zoster among users of statins; For studies that produced multiple publications, we included the article with the longest follow-up years or the largest number of incident cases. We identified articles that qualified for further examination by performing an initial screen of identified titles and abstracts, followed by a full-text review.

2.3 Data extraction
Two investigators independently extracted the following information from the studies: author, publish year, regions, study design, risk estimates (95% confidence interval [CI]),
mean age, follow-up years, female percentage, diagnosis of herpes zoster, assessment of using statins, types of statins, number of study participants (number of case and control for case-control studies, number of exposures and non-exposures for cohort studies) and confounder adjustment. If the information was unavailable or not clear from a published report, we collected relevant data by corresponding with the authors.

We used the Newcastle-Ottawa Quality Assessment Scale (NOS) to evaluate the study quality with consideration of the following aspects: selection, comparability, and exposure for non-randomized studies. For the case-control and cohort studies, different evaluation criteria were used. A total score of less than or equal to three was considered poor quality, four to six was considered moderate quality, and seven to nine was deemed high quality. Poor quality studies would be excluded in the sensitivity analysis.

2.4 Data synthesis and analysis

The fully adjusted risk estimates were used to estimate the association between statins and the risk of herpes zoster, and the hazard ratio (HR) and relative ratio (RR) values were regarded equivalent to odds ratio (OR) for the low incidence of diseases. Forest plots were made to visually assess the ORs and corresponding 95% CI across studies. Heterogeneity across studies was assessed by the Cochrane Q statistic (significance level of p <0.10) and the I² statistic (ranges from 0% to 100% with lower values representing less heterogeneity). The ORs were pooled using the DerSimonian and Laird inverse-variance-weighted random-effects models.

The influences of participants characteristics on the results were assessed by meta regression and subgroup analyses of study type, area, number of study participants,
follow-up time, female percentage, mean age, and quality of study. We omitted one study each time to test the influence of individual studies on the heterogeneity and the robustness of the results. The potential publication bias was examined by visual inspection of the funnel plot and the result of Egger’s test ($p < 0.10$).

The analyses were done with STATA version 14.1 (Stata Corp, College Station, Texas). A p-value $< 0.05$ was considered statistically significant, except where otherwise specified.

2.5 Patient and public involvement

patients and or public were not involved.

3. Results

3.1 Literature search

Two investigators independently performed eligibility assessment and data extraction and the results were compared and consensus was reached. The initial search yielded 174 articles. 13 duplicate articles were identified. An additional study was found by searching relevant messages in google scholar. After the first round of screening based on titles and abstracts, 14 articles were retained for further review. After detailed examination, 9 articles were excluded. Five studies were excluded because they were reviews, two studies were excluded because the data was not provided, one study was excluded because it was a conference abstract, and one study was excluded because it was a letter. Ultimately, we included five articles in the meta-analysis (Figure 1).
3.2 Study characteristics

The characteristics of the included five studies are presented in Table 1. Five studies were published between 2008 and 2016. Two studies were evaluated as high quality, and the rest were of moderate quality, no study was excluded for poor quality. Two studies were in Asia, two in North America, and one in Europe. The participants of one study were limited to veterans. Follow-up duration ranged from 1.95 to 8.6 years, with a median of 4.7 years. The mean age of participants was between 51.7-73 years, and the participants included in one study were all older than 66. The largest study had 694,295 participants and the smallest study included 18,951 participants. All studies had roughly the same ratio of sex of 50% except one study with only 3.3 percent women. Two studies included seven types of statins, two studies included six types of statins, one study included five types of statins. The diagnosis of HZ of included studies mostly relied on the International Classification of Diseases (ICD) code. The assessment of statins use in all studies relied on prescriptions or medication records. Adjustment for potential confounding factors differed between studies, and most risk estimates were adjusted for age and gender.

3.3 Statins and herpes zoster

Five studies were designed as retrospective studies. The majority of studies reported a positive association, and one study reported that the OR was not statistically different than 1.00. Three studies reported dose-response analysis, but the data could not be used for a dose-response meta-analysis due to different definitions of dose. Two of these studies, Matthews et al, [low dose, OR: 1.12 (95% CI: 1.10,1.14); medium dose, OR:
1.15 (95% CI: 1.11,1.18); high dose, OR:1.26 (95% CI: 1.15,1.39)] and Chen et al\textsuperscript{11} [low
dose, OR: 0.80 (95% CI: 0.76,0.85); high dose, OR: 2.96 (95% CI: 2.74,3.20)] showed
higher risk of herpes zoster infection in patients with receiving a higher dose. Antoniou et
al\textsuperscript{10} [medium dose, OR: 1.05 (95% CI: 1.00,1.10); high dose, OR:1.03 (95% CI:
0.90,1.19)] reported no appreciable difference in the risk of herpes zoster with dose\textsuperscript{10}.
Two studies\textsuperscript{11,12} reported the OR of males and females respectively, and one study reported
the OR of male was not statistically significant. The pooled OR from a random-effects
model of women was 1.32 (95% CI: 1.27-1.37, $I^2=0\%$), and the pooled OR from
random-effects model of men was 1.17 (95% CI: 1.05-1.31, $I^2=77\%$). Both male and
female patients had a higher risk of herpes zoster, and the women were little higher
relative to men. This result need to be further verified due to the small number of study
participants.

The adjusted OR (95% CI) related to herpes zoster was 1.17 (95% CI: 1.10-1. 24,
Figure 2). And we detected an obvious heterogeneity ($I^2=93\%$; $P <0.000$).

3.4 Publication bias

There was no publication bias based on visual inspection of the funnel plot (Figure 3) and
the result of Egger’s test ($p = 0.808$), but this analysis was based on only a few studies.

3.5 Meta regression, subgroup and sensitivity analyses

We conducted meta regression to try to ascertain the sources of heterogeneity, and the
results were shown in Table 2. The results suggested that study type might be the source
of the heterogeneity. Therefore, we conducted subgroup analyses by study type, area,
follow-up time, female percentage, the number of population, mean age and the quality of study (Table 3). The subgroup of area (Asia: $I^2=53\%$, OR: 1.26, 95% CI: 1.19-1.32; North America: $I^2=58\%$, OR: 1.08, 95% CI: 0.95-1.23), follow-up time ($\geq$5y: $I^2=59\%$, OR: 1.08, 95% CI: 0.95-1.23) and the number of study participants ($\geq$200 thousand: $I^2=0\%$, OR: 1.13, 95% CI: 1.11-1.15) exhibited marked decreases in heterogeneity. Therefore, we speculated that heterogeneity might derive from study area, follow-up time and the number of study participants. Besides, we found that there was no association (OR: 1.08, 95% CI: 0.95-1.23) between statins and risk of herpes zoster in North America participants with a longer follow-up time, but the results needed to be further verified due to the small number of studies in the subgroups.

A sensitivity analysis of omitting one study in each turn showed no substantial change on the results, and we found the study by Chung et al. was a major source of heterogeneity (from 93% to 52%).

4. Discussion

In this meta-analysis of approximately 700,000 cases and 1,200,000 controls, we demonstrated a significantly increased risk of herpes zoster with an overall 1.17-fold increased risk among patients who used statins compared with non-users.

HMG-CoA reductase, also known as statin, can exhibit some immunomodulatory effects, including improving epithelial cell function, reducing oxidative stress, and alleviating inflammation\textsuperscript{32,33}. Statins can impair T-cell activation and proliferation\textsuperscript{34,35}, and statins can also decrease some proinflammatory cytokines\textsuperscript{36,37}, potentially contributing to the susceptibility to herpes zoster. In contrast, one study showed that statins could
increase the number of Tregs in vivo\textsuperscript{38}, but a statin-induced increase in Tregs might lead to the reactivation of latent viral infections\textsuperscript{39,40}, like the varicella zoster virus. Obviously, a concrete mechanism has not been established, and more studies are needed.

We usually associate the use of statins with hyperlipidemia, but these studies did not assess serum cholesterol levels. This is called confounding by indication. Confounding by indication occurs when the effects of treatment indication are ignored, or in general, when factors that may be a consequence of a condition are instead treated as potential causes of that condition\textsuperscript{41}. A higher dose or longer course of treatment suggests more serious hyperlipidemia to some extent, and Chen et al.\textsuperscript{11} reported that younger statin users were at a higher risk of herpes zoster infection, however the major risk factor for herpes zoster is increasing age\textsuperscript{42,43}, so the results may reflect insufficient adjustment or the consumption by younger patients of a high fat diet with a high cholesterol level. Furthermore, one small study demonstrated that cholesterol levels were associated with herpes zoster in cardiac transplant recipients\textsuperscript{44}. Although no mechanism has been established, the range of serum cholesterol levels may be associated with the risk of herpes zoster. Statins are prescribed for both primary and secondary prevention of cardiovascular disease (CVD)\textsuperscript{45}, thus it is unclear if observed effects are due to CVD or the risk factors of CVD that increasing the risk of herpes zoster rather than the use of statins, though the studies included tried to adjust for partial risk factors. Additional studies are needed.

In our study, we found that gender might contribute to the risk of herpes zoster among statins users, though the effect was weak. Gender has already been identified as a risk factor of herpes zoster\textsuperscript{42,46}, and the use of statin might further increase the risk of
infection. The gender difference of infection may indicate effects of sex hormone\textsuperscript{47}, and statins can exert a regulating effect of estrogen receptor\textsuperscript{48}. Recently, the use of statins was linked to the occurrence of diabetes\textsuperscript{49} for patients with no history of diabetes, and the incidence of herpes zoster is reported much higher in patients with diabetes\textsuperscript{50,51}. Because women are more susceptible to diabetes, these factors may be related. Overall, more studies are needed to confirm the result.

This is the first systematic review and meta-analysis that specifically evaluated the association between statins use and the risk of herpes zoster. The studies included in our meta-analysis included many participants and had a long-term follow-up time, which improves the statistical power of the meta-analysis.

Several limitations of this meta-analysis should be acknowledged. First, this was a meta-analysis of observational studies so we could at best demonstrate an association but not a causal relationship. Second, we found a significant heterogeneity across studies, which might arise from regional differences, differences in the number of study participants and follow-up time. Additionally, the study by Chung et al. contributed much heterogeneity to the result. Third, we did not study the effects of different statins on risk of herpes zoster because of insufficient data. Fourth, the summary results might be influenced by the conversion of other measures to OR. Finally, more studies are needed for more robust analysis.

5. Conclusions

Our meta-analysis demonstrates a significantly elevated risk of herpes zoster among statins users, and further studies are warranted.
**Author contributions**

Xueqiang Guan designed the study. Lai lai Fan and Yangyang Wang completed the extraction and analysis of data. Lai lai Fan and Xiang Liu reviewed the results. Lai lai Fan wrote the report. All authors participated in the discussion and modification of the text. All authors approved the final version of the paper.
Reference

1. Johnston TP, Korolenko TA, Pirro M, et al. Preventing Cardiovascular Heart Disease: Promising Nutraceutical and non-Nutraceutical Treatments for Cholesterol Management. *Pharmacological Research* 2017;120:219-25.

2. Jasińska M, Owczarek J, Orszulakmichalak D. Statins: a new insight into their mechanisms of action and consequent pleiotropic effects. *Pharmacological Reports* 2007;59(5):483.

3. Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovascular Drugs and Therapy* 2005;19(6):403-14.

4. Draeger A, Monastyrskaya K, Mohaupt M, et al. Statin therapy induces ultrastructural damage in skeletal muscle in patients without myalgia. *Journal of Pathology* 2006;210(1):94-102.

5. Thompson PD, Panza G, Zaleski A, et al. Statin-Associated Side Effects. *Journal of the American College of Cardiology* 2016;67(20):2395-410.

6. Schmader K. Herpes Zoster. *Clinics in geriatric medicine* 2016;32(3):539-53. doi: 10.1016/j.cger.2016.02.011 [published Online First: 2016/07/10]

7. Cohen JI. Clinical practice: Herpes zoster. *New England Journal of Medicine* 2013;369(3):255-63.

8. Arnold N, Messaoudi I. Herpes zoster and the search for an effective vaccine. *Clinical & Experimental Immunology* 2017;187(1)

9. Keating GM. Shingles (Herpes Zoster) Vaccine (Zostavax ®): A Review in the Prevention of Herpes Zoster and Postherpetic Neuralgia. *Biodrugs Clinical Immunotherapeutics Biopharmaceuticals & Gene Therapy* 2016;30(3):243-54.

10. Antoniou T, Zheng H, Singh S, et al. Statins and the risk of herpes zoster: A population-based cohort study. *Pharmacoepidemiology and Drug Safety* 2013;22:309-10. doi: 10.1002/pds.3512

11. Chen HH, Lin CL, Yeh CJ, et al. Statins can increase the risk of herpes zoster infection in Asia. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2015;34(7):1451-8. doi: 10.1007/s10096-015-2372-3 [published Online First: 2015/04/13]

12. Chung SD, Tsai MC, Liu SP, et al. Herpes zoster is associated with prior statin use: a population-based case-control study. *PloS one* 2014;9(10):e111268. doi: 10.1371/journal.pone.0111268 [published Online First: 2014/10/25]

13. Matthews A, Turkson M, Forbes H, et al. Statin use and the risk of herpes zoster: a nested case-control study using primary care data from the U.K. Clinical Research Practice Datalink. *The British journal of dermatology* 2016;175(6):1183-94. doi: 10.1111/bjd.14815 [published Online First: 2016/11/03]

14. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Jama* 2000;283(15):2008-12.

15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology* 2010;25(9):603-05.

16. Margulis AV, Pladevall M, Rieraguardia N, et al. Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle–Ottawa Scale and the RTI item bank. *Clinical Epidemiology* 2014;6(8):359.

17. Higgins J, Al E. Measuring inconsistencies in meta-analyses. 2003
18. Dersimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;7(3):177-88.

19. Wang J, Shen Y, Wang J, et al. Relation of phosphodiesterase type 5 inhibitors and malignant melanoma: a meta-analysis and systematic review. *Oncotarget* 2017

20. Schnee S, Enoch M, Noriega-Crespo A, et al. Bias in meta-analysis detected by a simple, graphical test. *Bmj* 1997;315(7109):629.

21. Huang S, Yang Z, Ma Y, et al. miR-101 Enhances Cisplatin-Induced DNA Damage Through Decreasing Nicotinamide Adenine Dinucleotide Phosphate Levels by Directly Repressing Tp53-Induced Glycolysis and Apoptosis Regulator Expression in Prostate Cancer Cells. *DNA and cell biology* 2017;36(4):303-10. doi: 10.1089/dna.2016.3612 [published Online First: 2017/04/07]

22. Goldstein MR, Mascitelli L, Pezzetta F. The double-edged sword of statin immunomodulation. *International journal of cardiology* 2009;135(1):128-30. doi: 10.1016/j.ijcard.2008.01.023 [published Online First: 2008/05/20]

23. Kalra S, Chawla A. Herpes zoster and diabetes. *JPMA The Journal of the Pakistan Medical Association* 2016;66(8):1042-3. [published Online First: 2016/08/16]

24. Pirmohamed M. Statins, immunomodulation, and infections: a complex and unresolved relationship. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014;58(3):357-8. doi: 10.1093/cid/cit751 [published Online First: 2013/11/21]

25. Shalom G, Cohen AD. Statin exposure and the risk for herpes zoster: implications for public health. *The British journal of dermatology* 2016;175(6):1137-38. doi: 10.1111/bjd.15031 [published Online First: 2016/12/21]

26. Yuet WC, Khine H, Ahmad Z. Statin-associated adverse events. *Clinical Medicine Insights: Therapeutics* 2015;7:17-24. doi: 10.4137/CMT.S18865

27. McKinney WP, Horowitz MM, Battiola RJ. Susceptibility of hospital-based health care personnel to varicella-zoster virus infections. *American journal of infection control* 1989;17(1):26-30. [published Online First: 1989/02/01]

28. Terao M, Yamamoto T, Umeda J, et al. Drug induced herpes zoster (Do statin induce herpes zoster?). *Skin Research* 2005;4(4):335-38.

29. Cirillo DJ, Wallace RB. Statin use on incident immune-mediated and infectious conditions in the veterans administration health system. *Journal of General Internal Medicine* 2012;27:S309-S10.

30. Antoniou T, Juurlink DN, Mamdani MM, et al. Reply to Strandberg and Tienari. *Clinical Infectious Diseases* 2014;58(7):1043-44. doi: 10.1093/cid/ciu036

31. Cirillo DJ. The effect of statin use on incident immune-mediated and infectious conditions among U.S. veterans. *Dissertations & Theses - Gradworks* 2008

32. Laufs U, Liao JK. Isoprenoid metabolism and the pleiotropic effects of statins. *Current Atherosclerosis Reports* 2003;5(5):372-8.

33. Vishal T, Bano G, Khajuria V, et al. Pleiotropic effects of statins. *Annual Review of Pharmacology & Toxicology* 2005;45(4):89.

34. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nature Reviews Immunology* 2006;6(5):358.

35. Ghittoni R, Lazzerini PE, Pasini FL, et al. T lymphocytes as targets of statins: molecular mechanisms and therapeutic perspectives. *Inflammation & allergy drug targets* 2007;6(1):3-16.
36. Inhibition of proinflammatory cytokine production by pravastatin: The Lancet.

37. Rezaie-Majd A, Maca T, Bucek RA, et al. Simvastatin reduces expression of cytokines interleukin-6, interleukin-8, and monocyte chemoattractant protein-1 in circulating monocytes from hypercholesterolemic patients. Arteriosclerosis Thrombosis & Vascular Biology 2002;22(7):1194.

38. Mausner-Fainberg K, Luboshits G, Mor A, et al. The effect of HMG-CoA reductase inhibitors on naturally occurring CD4 + CD25 + T cells ☆. Atherosclerosis 2008;197(2):829.

39. Belkaid Y, Rouse BT. Natural regulatory T cells in infectious disease. Nature Immunology 2005;6(4):353.

40. Goldstein ML, Pezzetta F. The double-edged sword of statin immunomodulation. International Journal of Cardiology 2009;135(1):128.

41. Pbd BMPM, MPH TDKM, Lin D, et al. Assessment and Control for Confounding by Indication in Observational Studies. Journal of the American Geriatrics Society 1999;47(6):749–54.

42. Amicizia D, Domnich A, Arata L, et al. The role of age-sex interaction in the development of post-herpetic neuralgia. Human vaccines & immunotherapeutics 2017;13(2):376-78. doi: 10.1080/21645515.2017.1264799 [published Online First: 2017/02/22]

43. Blum A. HMG-CoA reductase inhibitors (statins), inflammation, and endothelial progenitor cells—New mechanistic insights of atherosclerosis. BioFactors (Oxford, England) 2014;40(3):295-302.

44. Del Pozo JL, Van dB, Mandrekar JN, et al. High serum cholesterol levels are associated with herpes zoster infection after heart transplantation. Clinical Infectious Diseases 2010;50(1):121-22.

45. Care NCCFP. Drug therapy for the primary prevention of cardiovascular disease (CVD): Royal College of General Practitioners (UK) 2008.

46. Opstelten W, Van Essen GA, Schellevis F, et al. Gender as an independent risk factor for herpes zoster: a population-based prospective study. Annals of Epidemiology 2006;16(9):692-95.

47. McClelland EE, Smith JM. Gender specific differences in the immune response to infection. Archivum Immunologiae et Therapiae Experimentalis 2011;59(3):203-13. doi: 10.1007/s00005-011-0124-3 [published Online First: 2011/03/29]

48. Taylor HS, Alderman M, D’Hooghe TM, et al. Effect of Simvastatin on Baboon Endometriosis. Biology of reproduction 2017 doi: 10.1093/biolre/iox058 [published Online First: 2017/06/24]

49. Ridker PM, Pradhan A, Macfadyen JG, et al. Cardiovascular Benefits and Diabetes Risks of Statin Therapy in Primary Prevention. Lancet 2012;56(6):565.

50. Amerio P, Innocente C, Feliciani C, et al. [Herpes zoster incidence in diabetic patients.]. Anales Del Sistema Sanitario De Navarra 2013;36(36):57-62.

51. Guignard AP, Greenberg M, Lu C, et al. Risk of herpes zoster among diabetics: a matched cohort study in a US insurance claim database before introduction of vaccination, 1997–2006. Infection 2014;42(4):729.
| Study Region Design | Study Region | Study Design | OR (95% CI) | Mean Age (years) | Follow-up (years) | Female (%) | Diagnosis of herpes zoster | Assessment of statins use | Types of statins | Number of study participants | Confounder adjustment | Quality assessment (NOS) |
|---------------------|--------------|--------------|------------|-----------------|------------------|------------|--------------------------|---------------------|-----------------|-----------------------------|---------------------|-------------------------|
| Matthews et al, 2016 | UK case-control | 1.13 (1.11, 1.15) | 59.5 | 8.6 | 60.7 | ICD code | prescription of a statin | atorvastatin, rosvastatin, cerivastatin, simvastatin, fluvastatin, pravastatin, lovastatin | 1,44,959/5,49,336 | BM, CVD, HIV, smoking, alcohol, RA, lymphoma, leukaemia, myeloma, HSCT, OIT, SLE, CKD, COPD, oral corticosteroids, OUCID, DM, asthma, depression, cancer. | Selection: 4 | Comparability: 2 |
| Chen et al, 2015 | Asia cohort | 1.21 (1.13, 1.29) | 60.1 | 4.82 | 50 | ICD code | prescription drug details | atorvastatin, rosvastatin, simvastatin, fluvastatin, pravastatin, lovastatin | 53,069/53,069 | age, sex, CCI score, and comorbidities, HPN, DM, IBD, stroke, cancer, SLE, RA, HIV | Selection: 3 | Comparability: 2 |
| Antoniou et al, 2014 | Canada cohort | 1.13 (1.10, 1.17) | 73 | 1.95 | 55.2 | ICD code or receipt of a prescription for either valaciclovir or famciclovir for the treatment of herpes zoster. | medication records | atorvastatin, rosvastatin, cerivastatin, simvastatin, fluvastatin, pravastatin, lovastatin | 4,94,651/4,94,651 | age, sex, CCI, CKD, residence, No. of prescription drugs in previous year, medication use, Income quintile, MI, angina, HPN, stroke, systemic malignancy, UC, Crohn’s disease, SLE, RA, HIV, CABG | Selection: 2 | Comparability: 2 |
| Chung et al, 2014 | China case-control | 1.28 (1.24, 1.32) | 51.7 | NA | 53.3 | ICD code | medical orders | atorvastatin, rosvastatin, | 47,359/1,42,077 | age, sex, index year, CHF, MI, liver | Selection: 3 | Comparability: 1 |
| Study               | Country | Study Design | RR (95% CI) | Sample Size | Sex | Race | Marital Status | Local VISN | Chronic Disease Score | Died During Follow-up | Prevalence of Elixhauser Conditions | Selection | Comparability | Outcome |
|---------------------|---------|--------------|-------------|-------------|-----|------|----------------|------------|----------------------|-----------------------|--------------------------------------|------------|---------------|---------|
| Cirillo et al, 2008 | US      | Case-control | 0.98 (0.82, 1.17) | 58          | 5.28 | 3.3  |                |            |                      |                       |                                      | 2          | 2             | 1       |

**Table 1: Characteristics of studies included in the meta-analysis of relation between statins use and herpes zoster.**
| Subgroup                        | $P_{\text(heterogeneity)}$ |
|--------------------------------|-----------------------------|
| Study type                     | 0.094                       |
| Area                           | 0.159                       |
| Follow-up time                 | 0.949                       |
| Female percentage              | 0.282                       |
| Number of study participants   | 0.760                       |
| Mean age                       | 0.596                       |
| Quality of study               | 0.731                       |

**Table 2: Meta regression of risk of herpes zoster among statins users.**
| Subgroup                      | OR (95% CI) | No. of studies | $I^2$ (%) | $P_{(heterogeneity)}$ |
|-------------------------------|-------------|---------------|-----------|----------------------|
| **Study type**                |             |               |           |                      |
| case-control                  | 1.15 (1.03, 1.29) | 3 [12, 13, 31] | 96        | <0.00                |
| cohort                        | 1.16 (1.09, 1.24) | 2 [10, 11]    | 70        | 0.07                 |
| **Area**                      |             |               |           |                      |
| Asia                          | 1.26 (1.19, 1.32) | 2 [11, 12]    | 53        | 0.14                 |
| North America                 | 1.08 (0.95, 1.23) | 2 [10, 31]    | 58        | 0.12                 |
| Europe                        | 1.13 (1.11, 1.15) | 1 [13]        | NA        | NA                   |
| **Follow-up time**            |             |               |           |                      |
| ≥5y                           | 1.08 (0.95, 1.23) | 2 [13, 31]    | 59        | 0.12                 |
| <5y                           | 1.16 (1.09, 1.24) | 2 [10, 11]    | 70        | 0.07                 |
| **Female percentage**         |             |               |           |                      |
| ≥50%                          | 1.18 (1.11, 1.26) | 4 [10-13]     | 94        | <0.00                |
| <50%                          | 0.98 (0.82, 1.17) | 1 [31]        | NA        | NA                   |
| **Number of study participants** |           |               |           |                      |
| ≥200 thousand                 | 1.13(1.11, 1.15) | 2 [10, 13]    | 0         | 1.00                 |
| <200 thousand                 | 1.19(1.09, 1.31) | 3 [11, 12, 31]| 80        | 0.007                |
| **Mean age**                  |             |               |           |                      |
| ≥60 years                     | 1.16 (1.09, 1.24) | 2 [10, 11]    | 70        | 0.07                 |
| <60 years                     | 1.15 (1.03, 1.29) | 3 [12, 13, 31]| 96        | <0.00                |
| **Quality of study**          |             |               |           |                      |
| high                          | 1.16 (1.09, 1.24) | 2 [11, 13]    | 72        | 0.06                 |
| moderate                      | 1.15 (1.03, 1.29) | 3 [10, 12, 31]| 95        | <0.00                |

*A total score of 4-6 was considered moderate quality, and 7-9 was deemed high quality;

Table 3: Subgroup analyses of risk of herpes zoster among statins users.
The related literatures were obtained from the database (n=185, pubmed=23, embase=162)

Get related literature by other resources (n=1)

Duplicates excluded (n=13)

Abstracts reviewed (n=173)

No related literature (n=159)

Full text studies reviewed (n=14)

9 articles excluded review (n=5) no relevant outcome (n=2) conference abstract (n=1) letter (n=1)

Articles accepted for analysis (n=5)

Flow chart of the meta-analysis of association between statins use and herpes zoster.

173x169mm (300 x 300 DPI)
Forest plot of the meta-analysis of association between statins use and herpes zoster.

182x123mm (300 x 300 DPI)
Funnel plot of the meta-analysis of association between statins use and herpes zoster.
Search strategies in Pubmed

#1. ((((((exp Herpes Zoster[Title/Abstract]) OR Herpesvirus 3,
    Human[Title/Abstract]) OR shingles[Title/Abstract]) OR zoster[Title/Abstract])
OR Varicellovirus[Title/Abstract]) OR varicellovir*[Title/Abstract]) OR
((hhv3[Title/Abstract] OR hhv-3[Title/Abstract])) OR "Herpes Zoster"[Mesh])

#2. ((((Hydroxymethylglutaryl-CoA Reductase Inhibitors[Title/Abstract]) OR hydroxymethylglutaryl-CoA reductase inhibitor*[Title/Abstract])
OR statin*[Title/Abstract]) OR atorvastatin[Title/Abstract]) OR
cerivastatin[Title/Abstract]) OR dalvastatin[Title/Abstract]) OR
fluindostatin[Title/Abstract]) OR fluvastatin[Title/Abstract]) OR
lovastatin[Title/Abstract]) OR pitavastatin[Title/Abstract]) OR
pravastatin[Title/Abstract]) OR rosuvastatin[Title/Abstract]) OR
simvastatin[Title/Abstract]) OR ((meglutol[Title/Abstract] OR
mevinolin*[Title/Abstract] OR monacolin*[Title/Abstract] OR
pravachol[Title/Abstract] OR lipex[Title/Abstract] OR lipitor[Title/Abstract] OR
zocor[Title/Abstract] OR mevacor[Title/Abstract] OR lescol[Title/Abstract] OR
baycol[Title/Abstract])) OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"
[Pharmacological Action])

#3. #1 AND #2
Search strategies in Emabase

#1. 'herpes zoster'/exp OR 'varicella zoster virus':ab,ti OR shingles:ab,ti OR
zoster:ab,ti OR (varicella NEAR/3 virus*):ab,ti OR varicellovirus:ab,ti OR
varicellovir*:ab,ti OR 'hhv 3':ab,ti OR hhv3:ab,ti

#2. ('hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp OR 'hmg coa
reductase inhibitor*':ab,ti OR 'hmg co a reductase inhibitor*':ab,ti OR
statin*:ab,ti OR atorvastatin:ab,ti OR cerivastatin:ab,ti OR dalvastatin:ab,ti OR
fluindostatin:ab,ti OR fluvastatin:ab,ti OR lovastatin:ab,ti OR pitavastatin:ab,ti
OR pravastatin:ab,ti OR simvastatin:ab,ti OR rosuvastatin:ab,ti OR
meglutol:ab,ti OR mevinolin*:ab,ti OR monacolin*:ab,ti OR pravachol:ab,ti OR
lipex:ab,ti OR lipitor:ab,ti OR zocor:ab,ti OR mevacor:ab,ti OR lescol:ab,ti OR
baycol:ab,ti)

#3. #1 AND #2
Association between statin use and herpes zoster: A systematic review and meta-analysis

| Journal: | BMJ Open |
| --- | --- |
| Manuscript ID: | bmjopen-2018-022897.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 06-Aug-2018 |
| Complete List of Authors: | fan, lai; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, urology Wang, Yang-Yang; Wenzhou Medical University Second Affiliated Hospital, rehabilitation liu, xiang; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, urology guan, qiang; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Cardiology |
| Primary Subject Heading: | Infectious diseases |
| Secondary Subject Heading: | Cardiovascular medicine, Infectious diseases |
| Keywords: | herpes zoster, statins, meta-analysis |
Association between statin use and herpes zoster: A systematic review and meta-analysis

Lailai Fan MD², Yangyang Wang MD³, Xiang Liu MD², Xueqiang Guan MD¹

1. Department of Cardiology, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, Xueyuanxi Road, No. 109, Wenzhou, Zhejiang 325000, China.
2. Department of urology, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University.
3. Department of rehabilitation, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University.

Correspondence should be addressed to Xueqiang Guan; wzsgxq@163.com

Funding source: None.

Data sharing statement: All relevant study data can be found in the online supplementary files.

Acknowledgements: We acknowledge that the Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University for supporting the work of our study.

Competing Interests: None.
Abstract

**Objective**—Statins are commonly prescribed worldwide. In addition to being potent lipid-lowering agents, statins have immunomodulating properties that may increase the risk of varicella-zoster virus reactivation. This adverse effect may have substantial public health implications.

**Design**—We performed a meta-analysis of observational studies to assess the association between statin use and the risk of herpes zoster infection. We searched PubMed, EMBASE, Web of Science, and Cochrane databases to identify studies published from 1980 to 2018. The multivariate-adjusted odds ratios (ORs) were pooled using random-effect models, and subgroup and sensitivity analyses were performed to examine the source of heterogeneity.

**Result**—Six studies were analyzed, with a total of more than two million participants. We determined if the use of statins might increase the risk of infection of herpes zoster (OR:1.18, 95% confidence interval [CI]: 1.11-1.25). We detected significant heterogeneity ($I^2=91.2%$; $P<0.000$), and determined that the heterogeneity arises from regional differences.

**Conclusion**—The use of statins may increase the risk of herpes zoster infection. Because the studies included are limited and there may be potential bias, further studies are warranted.
Strengths and limitations of this study

1. We performed a comprehensive systematic search for eligible studies. This is the first systematic review and meta-analysis to specifically evaluated the association between statin use and the risk of herpes zoster.

2. The studies included in our meta-analysis included many participants with long-term follow-up time. Literature eligibility was assessed by two investigators independently. No significant publication bias was found.

3. This was a meta-analysis of observational studies, allowing the conclusion that an association exists, but this type of analysis cannot determine if a causal relationship exists.

4. We found significant heterogeneity across studies, due to regional differences. The study by Chung et al. contributed much heterogeneity, but the result remained significant after exclusion of this study.

5. We did not study the effects of different statins on the risk of herpes zoster due to insufficient data. Some results might be influenced by the conversion of other measures to OR.
1. Introduction

Statins (3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors) are used to lower levels of low-density lipoprotein cholesterol, and are widely prescribed for the prevention of cardiovascular diseases (CVD)\(^1\)\(^2\). In addition to acting as potent lipid-lowering agents, statins have immunomodulating properties that may increase the risk of infectious diseases\(^3\)\(^4\).

Herpes zoster occurs as a reactivation of a latent infection with varicella-zoster virus (VZV), causing post-herpetic neuralgia and acute and chronic pain\(^5\). The pain caused by inflammation and neuronal destruction can be disruptive to daily activities, decreasing quality of life for the elderly\(^6\). As statins are commonly prescribed worldwide, if statin use increases the risk of VZV reactivation, this adverse effect may present substantial public health implications.

Many epidemiological studies have reported an association between statin use and the risk of herpes zoster\(^7\)\(^-\)\(^12\), but there has been no meta-analysis to systematically evaluate all available data. To address this need, we conducted a comprehensive systematic review and meta-analysis of observational studies to assess the association between statin use and the risk of herpes zoster.

2. Methods

2.1 Search strategy

We followed the guidelines described in the Meta-Analysis of Observational Studies in Epidemiology (MOOSE)\(^13\). We first systematically searched PubMed and EMBASE databases on December 20, 2015 for studies of the association between statins and herpes
zoster. To ensure our study included all available up-to-date results, we systematically did an additional database search of PubMed, EMBASE, Web of Science, and Cochrane on July 20, 2018. We also checked the references of included studies and reviews. The search focused on statins and herpes zoster as subject terms and keywords. The detailed search strategies are shown in the Supplemental Material 1.

2.2 Study selection
Two investigators independently assessed literature eligibility, and disagreements were settled by discussion and consensus. Articles were included in the systematic review if: (1) the authors reported data from an original, peer-reviewed study (i.e., not review articles or conference abstracts); (2) the study was a cohort study or case-control study (case reports were not included due to a lower quality of evidence-based medical evidence); and (3) the authors reported risk estimates of herpes zoster among users of statins. For studies that resulted in multiple publications, we included the article with the longest follow-up time or that presented the most incident cases. We identified articles that qualified for further examination by performing an initial screen of identified titles and abstracts, followed by a full-text review.

2.3 Data extraction
Two investigators independently extracted the following information from the studies: authors, publication year, study region, study design, risk estimates (95% confidence interval [CI]), patient mean age, follow-up time or study period, female percentage, diagnosis of herpes zoster, assessment of the use of statins, types of statins used, number
of study participants (number of case participants and control participants for case-control studies, and the number of exposures and non-exposures for cohort studies), and confounder adjustment. If any information was unavailable or not clear from a published report, we collected the relevant data by directly corresponding with the authors.

We used the Newcastle-Ottawa Quality Assessment Scale (NOS)\textsuperscript{14} to evaluate the quality of each study with consideration of selection, comparability, and exposure for non-randomized studies\textsuperscript{15}. For the case-control and cohort studies, different evaluation criteria were used. A total score of less than or equal to three was considered poor quality, a score of four to six was considered moderate quality, and a score of seven to nine was deemed high quality. Poor quality studies were excluded in the sensitivity analysis. The details of study assessment are presented in Supplemental Material 2.

2.4 Data synthesis and analysis
The fully adjusted risk estimates were used to estimate the association between statin use and the risk of herpes zoster. The hazard ratio (HR) and relative ratio (RR) values were regarded equivalent to the odds ratio (OR) for the low incidence of diseases. Forest plots were made to visually assess the ORs and the corresponding 95\% CI across studies. The heterogeneity across studies was assessed by the Cochrane Q statistic (using a significance level of $p < 0.10$) and the $I^2$ statistic (this parameter ranges from 0\% to 100\% with lower values corresponding to less heterogeneity)\textsuperscript{16}. The ORs were pooled using the DerSimonian and Laird inverse-variance-weighted random-effects models\textsuperscript{17}. 
The influences of participant characteristics on the results were assessed by subgroup analyses of study type, study region, number of study participants, female percentage, mean age, and the quality of the study. We omitted each study individually to test the influence of studies on the heterogeneity and the robustness of the analysis\textsuperscript{18}. The potential publication bias was examined by visual inspection of the funnel plot and the Egger’s test result (p < 0.10)\textsuperscript{19}.

The analyses were performed with STATA version 14.1 (Stata Corp, College Station, Texas). A p-value < 0.05 was considered statistically significant, except where otherwise specified\textsuperscript{20}.

2.5 Patient and public involvement

No patients and/or the general public were involved in this study.

3. Results

3.1 Literature search

Two investigators independently assessed study eligibility and performed data extraction. The results were compared, discussed, and consensus was reached. The initial search yielded 249 articles. Among these, 38 duplicate articles were identified. An additional study was identified by a search of Google Scholar using search terms stains and herpes zoster. After the first round of screening based on titles and abstracts, 15 articles were retained and subjected to further review. After detailed examination, nine articles were excluded\textsuperscript{21-29}. Seven studies were excluded because they were reviews, one study was
excluded because it was a conference abstract, and one study was excluded because it was a letter. Ultimately, we included six articles\textsuperscript{7-12} in the meta-analysis (Figure 1).

3.2 Study characteristics

The characteristics of the included six studies are presented in Table 1. The six studies were published between 2008 and 2018. Two studies were evaluated as high quality\textsuperscript{11,12}, and the rest were of moderate quality; no study was excluded for poor quality. Three studies were performed in Asia\textsuperscript{8,9,11}, two in North America\textsuperscript{7,10}, and one in Europe\textsuperscript{12}. The participants of one study were limited to veterans\textsuperscript{10}. Follow-up duration ranged from 1.95 to 11 years, with a median of 5.9 years. The mean age of study participants was between 51.7-73 years, and the participants included in one study were all older than 66\textsuperscript{7}. The largest study\textsuperscript{12} included 694,295 participants, and the smallest study\textsuperscript{10} included 18,951 participants. All studies had roughly a 50% sex ratio except one study with only 3.3 percent women\textsuperscript{10}. Three studies\textsuperscript{7,11,12} included seven types of statins, two studies\textsuperscript{8,9} included six types of statins, and one study\textsuperscript{10} included five types of statins. In the included studies, the diagnosis of herpes zoster all relied on the International Classification of Diseases (ICD) code. The assessment of stain use relied on prescriptions or medication records. The adjustment for potential confounding factors differed between studies, and most risk estimates were adjusted for age and gender.

3.3 Statins and herpes zoster

The majority of studies reported a positive association, only one study reported an OR value that was not statistically different than 1.00\textsuperscript{10}. Three studies reported dose-response
analysis\cite{7,8,12}, but the data could not be utilized in a dose-response meta-analysis due to different definitions of dose in the different studies. Two of these studies, Matthews et al\cite{12} [low dose, OR: 1.12 (95% CI: 1.10-1.14); medium dose, OR: 1.15 (95% CI: 1.11-1.18); high dose, OR:1.26 (95% CI: 1.15-1.39)] and Chen et al\cite{11} [low dose, OR: 0.80 (95% CI: 0.76-0.85); high dose, OR: 2.96 (95% CI: 2.74-3.20)] showed a higher risk of herpes zoster infection in patients that received a higher dose. Antoniou et al\cite{7} [medium dose, OR: 1.05 (95% CI: 1.00-1.10); high dose, OR:1.03 (95% CI: 0.90-1.19)] reported no appreciable difference in the risk of herpes zoster with stain dose\cite{7}. Two studies\cite{8,9} reported separate OR calculations for males and females, and one study reported a OR value for male participants that was not statistically significant. The pooled OR from a random-effects model of women was 1.32 (95% CI: 1.27-1.37, $I^2=0\%$), and the pooled OR from a random-effects model of men was 1.17 (95% CI: 1.05-1.31, $I^2=77\%$). Both male and female patients exhibited a higher risk of herpes zoster, with a slightly higher risk for women. This result needs to be further verified due to the small number of study participants.

The adjusted OR (95% CI) value related to herpes zoster was determined as 1.18 (95% CI: 1.11-1.25, Figure 2). Additionally, we detected an obvious heterogeneity ($I^2=91.2\%$; $P <0.000$).

### 3.4 Publication bias

There was no publication bias based on visual inspection of the funnel plot (Figure 3) and the result of Egger’s test ($p =0.646$).
3.5 Subgroup and sensitivity analyses

We conducted subgroup analyses to try to identify the sources of heterogeneity. Analyses were performed by study type, study region, percentage of female, the number of study participants, participant mean age, and the quality of study (Table 2). The subgroup of study region (Asia: $I^2=11\%$, OR:1.26, 95% CI: 1.22-1.30; North America: $I^2=58\%$, OR:1.08, 95% CI: 0.95-1.23) exhibited marked decreases in heterogeneity. Therefore, we speculated that heterogeneity derives from regional differences. We found no association (OR: 1.08, 95% CI: 0.95-1.23) between statin use and risk of herpes zoster in North America participants, but these results needed to be further verified due to the small number of studies in the different subgroups.

We performed a sensitivity analysis by sequentially omitting each study and then determining if the removal of the study led to a substantial change in the results. We found the study by Chung et al. was a major source of heterogeneity (from 93% to 65%). We omitted this study, performed the analysis again, and found that the result was still significant (OR: 1.15, 95% CI: 1.11-1.19).

4. Discussion

In this meta-analysis of results from more than two million participants, we demonstrated a significantly increased risk of herpes zoster with an overall 1.18-fold increased risk among patients who used statins compared with non-users.

Stains can exhibit some immunomodulatory effects, including improving epithelial cell function, reducing oxidative stress, and alleviating inflammation\textsuperscript{30 31}. Statins can impair T-cell activation and proliferation\textsuperscript{32 33}, and statins can also decrease levels of some
proinflammatory cytokines\textsuperscript{34,35}, potentially affecting the susceptibility to herpes zoster. One study showed that statins could increase the number of regulatory T cells (Tregs) in vivo\textsuperscript{36}, but a statin-induced Tregs increase may lead to the reactivation of latent viral infections\textsuperscript{37,38}, like the varicella zoster virus. Overall, the detailed mechanism of how statin use affects varicella zoster virus remains unclear, and more studies are needed.

We typically associate the use of statins with hyperlipidemia, but most studies did not assess serum cholesterol levels. This may lead to confounding by indication. Confounding by indication occurs if the effects of treatment indication are ignored, or if factors that may be a consequence of a condition are instead treated as potential causes of that condition\textsuperscript{39}. A higher dose or longer course of treatment suggests the presence of more serious hyperlipidemia. Although Chen et al.\textsuperscript{8} reported that younger statin users exhibited a higher risk of herpes zoster infection, the major risk factor for herpes zoster is increasing age\textsuperscript{40,41}, so the differing results may reflect insufficient adjustment or the consumption by younger patients of a high fat diet leading to high cholesterol level. Furthermore, one study with few participants found that cholesterol levels were associated with herpes zoster in cardiac transplant recipients\textsuperscript{42}. Although no mechanism has been established, serum cholesterol levels may be associated with the risk of herpes zoster. Statins are prescribed for both primary and secondary CVD\textsuperscript{43}, so it is unclear if the observed effects are due to the presence of CVD or the risk factors of CVD that increase herpes zoster risk rather than the use of statins. Although these studies tried to adjust for partial risk factors, additional studies are needed.

In our analysis, we found a potential contribution of gender to the risk of herpes zoster among statin users, though the effect was weak. Gender was previously identified
as a risk factor of herpes zoster\textsuperscript{40,44}, and the use of statins might further increase the risk of infection. The gender difference for infection may indicate effects of sex hormones\textsuperscript{45}, consistent with the ability of statins to regulate the estrogen receptor\textsuperscript{46}. Recently, the use of statins was linked to the occurrence of diabetes\textsuperscript{47} for patients with no history of diabetes, and the incidence of herpes zoster has been reported to be much higher in patients with diabetes\textsuperscript{48,49}. Because women are generally more susceptible to diabetes, these factors may be related. Again, more studies with a large number of participants are needed to confirm the result.

The strengths of our study include the following: we performed a comprehensive systematic search for eligible studies; this is the first systematic review and meta-analysis to specifically evaluated the association between statin use and the risk of herpes zoster; the studies included in our meta-analysis included many participants with long-term follow-up time; literature eligibility was assessed by two investigators independently; no significant publication bias was found.

Several limitations of this meta-analysis should be acknowledged. First, this was a meta-analysis of observational studies, allowing the conclusion that an association exists, but this type of analysis cannot determine if a causal relationship exists. Second, we found significant heterogeneity across studies, due to regional differences. Additionally, the study by Chung et al. contributed much heterogeneity, but the result remained significant after exclusion of this study. Third, we did not study the effects of different statins on the risk of herpes zoster due to insufficient data. Fourth, some results might be influenced by the conversion of other measures to OR. Overall, more studies are needed for more robust analysis.
5. Conclusions

Our meta-analysis indicates that the use of statins may increase the risk of herpes zoster. Because the studies included are limited and there is potential bias, further studies are warranted.

Figure legends

Figure 2: The squares and horizontal lines correspond to the study-specific OR and 95% CIs. The area of the squares reflects the study-specific weight. Weights are from random effects analysis. The diamond represents the pooled OR and 95% CI.

Figure 3: Circles represent identified studies.

Author contributions

Xueqiang Guan designed the study. Lailai Fan and Yangyang Wang completed the extraction and analysis of data. Lailai Fan and Xiang Liu reviewed the results. Lailai Fan wrote the report. All authors participated in the discussion and modification of the text. All authors approved the final version of the paper.
Reference

1. Johnston TP, Korolenko TA, Pirro M, et al. Preventing Cardiovascular Heart Disease: Promising Nutraceutical and non-Nutraceutical Treatments for Cholesterol Management. *Pharmacological Research* 2017;120:219-25.

2. Jasińska M, Owczarek J, Orszulakmichalak D. Statins: a new insight into their mechanisms of action and consequent pleiotropic effects. *Pharmacological Reports* 2007;59(5):483.

3. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nature Reviews Immunology* 2006;6(5):358-70.

4. Neuhaus O, Strasserfuchs S, Fazekas F, et al. Statins as immunomodulators: comparison with interferon-beta 1b in MS. *Neurology* 2002;59(7):990-7.

5. ZOSTER EOH. Herpes zoster and postherpetic neuralgia. *Essentials of Pain Medicine E-book* 2011:358.

6. Schmader K. Herpes Zoster. *Clinics in geriatric medicine* 2016;32(3):539-53. doi: 10.1016/j.cger.2016.02.011 [published Online First: 2016/07/10]

7. Antoniou T, Zheng H, Singh S, et al. Statins and the risk of herpes zoster: A population-based cohort study. *Pharmacoepidemiology and Drug Safety* 2013;22:309-10. doi: 10.1002/pds.3512

8. Chen HH, Lin CL, Yeh CJ, et al. Statins can increase the risk of herpes zoster infection in Asia. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2015;34(7):1451-8. doi: 10.1007/s10096-015-2372-3 [published Online First: 2015/04/13]

9. Chung SD, Tsai MC, Liu SP, et al. Herpes zoster is associated with prior statin use: a population-based case-control study. *PloS one* 2014;9(10):e111268. doi: 10.1371/journal.pone.0111268 [published Online First: 2014/10/25]

10. Cirillo DJ. The effect of statin use on incident immune-mediated and infectious conditions among U.S. veterans. *Dissertations & Theses - Gradworks* 2008

11. Kim MC, Yun SC, Lee SO, et al. Statins increase the risk of herpes zoster: A propensity score-matched analysis. *PloS one* 2018;13(6):e0198263. doi: 10.1371/journal.pone.0198263 [published Online First: 2018/06/15]

12. Matthews A, Turkson M, Forbes H, et al. Statin use and the risk of herpes zoster: a nested case-control study using primary care data from the U.K. Clinical Research Practice Datalink. *The British journal of dermatology* 2016;175(6):1183-94. doi: 10.1111/bjd.14815 [published Online First: 2016/11/03]
13. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Jama* 2000;283(15):2008-12.

14. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology* 2010;25(9):603-05.

15. Margulis AV, Pladevall M, Rieraguardia N, et al. Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle–Ottawa Scale and the RTI item bank. *Clinical Epidemiology* 2014;6(8):359.

16. Higgins J, Al E. Measuring inconsistencies in meta-analyses. 2003

17. Dersimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;7(3):177-88.

18. Wang J, Shen Y, Wang J, et al. Relation of phosphodiesterase type 5 inhibitors and malignant melanoma: a meta-analysis and systematic review. *Oncotarget* 2017

19. Schnee S, Enoch M, Noriega-Crespo A, et al. Bias in meta-analysis detected by a simple, graphical test. *Bmj* 1997;315(7109):629.

20. Huang S, Yang Z, Ma Y, et al. miR-101 Enhances Cisplatin-Induced DNA Damage Through Decreasing Nicotinamide Adenine Dinucleotide Phosphate Levels by Directly Repressing Tp53-Induced Glycolysis and Apoptosis Regulator Expression in Prostate Cancer Cells. *DNA and cell biology* 2017;36(4):303-10. doi: 10.1089/dna.2016.3612 [published Online First: 2017/04/07]

21. Goldstein MR, Mascitelli L, Pezzetta F. The double-edged sword of statin immunomodulation. *International journal of cardiology* 2009;135(1):128-30. doi: 10.1016/j.ijcard.2008.01.023 [published Online First: 2008/05/20]

22. Kalra S, Chawla A. Herpes zoster and diabetes. *JPMA The Journal of the Pakistan Medical Association* 2016;66(8):1042-3. [published Online First: 2016/08/16]

23. Pirmohamed M. Statins, immunomodulation, and infections: a complex and unresolved relationship. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014;58(3):357-8. doi: 10.1093/cid/cit751 [published Online First: 2013/11/21]

24. Shalom G, Cohen AD. Statin exposure and the risk for herpes zoster: implications for public health. *The British journal of dermatology* 2016;175(6):1137-38. doi: 10.1111/bjd.15031 [published Online First: 2016/12/21]

25. Yuet WC, Khine H, Ahmad Z. Statin-associated adverse events. *Clinical Medicine Insights: Therapeutics* 2015;7:17-24. doi: 10.4137/CMT.S18865

26. McKinney WP, Horowitz MM, Battiola RJ. Susceptibility of hospital-based health care personnel to
varicella-zoster virus infections. *American journal of infection control* 1989;17(1):26-30. [published Online First: 1989/02/01]

27. Terao M, Yamamoto T, Umeda J, et al. Drug induced herpes zoster (Do statin induce herpes zoster?). *Skin Research* 2005;4(4):335-38.

28. Cirillo DJ, Wallace RB. Statin use on incident immune-mediated and infectious conditions in the veterans administration health system. *Journal of General Internal Medicine* 2012;27:S309-S10.

29. Antoniou T, Juurlink DN, Mamdani MM, et al. Reply to Strandberg and Tienari. *Clinical Infectious Diseases* 2014;58(7):1043-44. doi: 10.1093/cid/ciu036

30. Laufs U, Liao JK. Isoprenoid metabolism and the pleiotropic effects of statins. *Current Atherosclerosis Reports* 2003;5(5):372-8.

31. Vishal T, Bano G, Khajuria V, et al. Pleiotropic effects of statins. *Annual Review of Pharmacology & Toxicology* 2005;45(4):89.

32. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nature Reviews Immunology* 2006;6(5):358.

33. Ghittoni R, Lazzerini PE, Pasini FL, et al. T lymphocytes as targets of statins: molecular mechanisms and therapeutic perspectives. *Inflammation & allergy drug targets* 2007;6(1):3-16.

34. Inhibition of proinflammatory cytokine production by pravastatin : The Lancet.

35. Rezaiemajd A, Maca T, Bucek RA, et al. Simvastatin reduces expression of cytokines interleukin-6, interleukin-8, and monocyte chemoattractant protein-1 in circulating monocytes from hypercholesterolemic patients. *Arteriosclerosis Thrombosis & Vascular Biology* 2002;22(7):1194.

36. Mausner-Fainberg K, Luboshits G, Mor A, et al. The effect of HMG-CoA reductase inhibitors on naturally occurring CD4 + CD25 + T cells ☆. *Atherosclerosis* 2008;197(2):829.

37. Belkaid Y, Rouse BT. Natural regulatory T cells in infectious disease. *Nature Immunology* 2005;6(4):353.

38. Goldstein ML, Pezzetta F. The double-edged sword of statin immunomodulation. *International journal of cardiology* 2009;135(1):128.

39. PbD BMPM, MPH TDKM, Lin D, et al. Assessment and Control for Confounding by Indication in Observational Studies. *Journal of the American Geriatrics Society* 1999;47(6):749–54.

40. Amicizia D, Domnich A, Arata L, et al. The role of age-sex interaction in the development of post-herpetic neuralgia. *Human vaccines & immunotherapeutics* 2017;13(2):376-78. doi: 10.1080/21645515.2017.1264799 [published Online First: 2017/02/22]

41. Blum A. HMG-CoA reductase inhibitors (statins), inflammation, and endothelial progenitor
42. Del Pozo JL, Van dBD, Mandrekar JN, et al. High serum cholesterol levels are associated with herpes zoster infection after heart transplantation. *Clinical Infectious Diseases* 2010;50(1):121-22.

43. Care NCCFP. Drug therapy for the primary prevention of cardiovascular disease (CVD): Royal College of General Practitioners (UK) 2008.

44. Opstelten W, Van Essen GA, Schellevis F, et al. Gender as an independent risk factor for herpes zoster: a population-based prospective study. *Annals of Epidemiology* 2006;16(9):692-95.

45. McClelland EE, Smith JM. Gender specific differences in the immune response to infection. *Archivum immunologiae et therapiae experimentalis* 2011;59(3):203-13. doi: 10.1007/s00005-011-0124-3 [published Online First: 2011/03/29]

46. Taylor HS, Alderman M, D’Hooghe TM, et al. Effect of Simvastatin on Baboon Endometriosis. *Biology of reproduction* 2017 doi: 10.1093/biolre/iox058 [published Online First: 2017/06/24]

47. Ridker PM, Pradhan A, Macfadyen JG, et al. Cardiovascular Benefits and Diabetes Risks of Statin Therapy in Primary Prevention. *Lancet* 2012;56(6):565.

48. Amerio P, Innocente C, Feliciani C, et al. [Herpes zoster incidence in diabetic patients.]. *Anales Del Sistema Sanitario De Navarra* 2013;36(36):57-62.

49. Guignard AP, Greenberg M, Lu C, et al. Risk of herpes zoster among diabetics: a matched cohort study in a US insurance claim database before introduction of vaccination, 1997–2006. *Infection* 2014;42(4):729.
| ICD code | prescription | Count         | Ratio (95% CI) | Propensity-score matching: | Selection: | Comparability: | Outcome: |
|----------|--------------|---------------|----------------|---------------------------|------------|----------------|----------|
|          | atorvastatin, rosvastatin, pitavastatin, simvastatin, fluvastatin, pravastatin, lovastatin | 25,726/25,726 | 1.25 (1.15-1.37) | age, gender, economic class, HPN, diabetes, dyslipidemia, IHD, TIA, HF, AF, VHD, carotid stenosis, PVD, CRD, CLD, CPD, RA, IBD, malignancy, transplantation recipients of solid organs or HSCT, HIV, depression | 3          | 2              | 2        |
|          | atorvastatin, rosvastatin, cerivastatin, simvastatin, fluvastatin, pravastatin, lovastatin | 1,44,959/5,49,336 | 1.13 (1.11,1.15) | BMI, CVD, HIV, smoking, alcohol, RA, lymphoma, leukemia, myeloma, HSCT, OIT, SLE, CKD, COPD, oral corticosteroids, OUCID, DM, asthma, depression, cancer. | 3          | 2              | 2        |
|          | atorvastatin, rosvastatin, simvastatin, fluvastatin, pravastatin, lovastatin | 53,069/53,069 | 1.21 (1.13,1.29) | age, sex, CCI score, and comorbidities, HPN, DM, IBD, stroke, cancer, SLE, RA, HIV | 3          | 2              | 1        |
| ICD code | medical orders | atorvastatin, rosuvastatin, simvastatin, fluvastatin, pravastatin, lovastatin | 47,359/1,42,077 | 1.28(1.24,1.32) | age, sex, index year, CHF, MI, liver disease, cancer, dementia, monthly income, geographic location | Selection: 2 | Comparability: 2 | Outcome: 2 |
|---|---|---|---|---|---|---|---|---|
| ICD code | prescription | atorvastatin, simvastatin, fluvastatin, pravastatin, lovastatin | 8,221/10,730 | 0.98(0.82,1.17) | sex, race, marital status, local VISN, means test, group, chronic disease score, died during follow-up, prevalence of elixhauser conditions | Selection: 2 | Comparability: 2 | Outcome: 1 |

AF: atrial fibrillation; VHD: valvular heart disease; PVD: peripheral vascular disease; CRD: chronic renal disease; CLD: chronic liver disease; CPD: chronic HSCT: haematopoietic stem cell transplantation; HIV: human immunodeficiency virus; BMI: body mass index; OIT: other immunosuppressive therapy; OUCID: other SLE: systemic lupus erythematosus; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CCI: Charlson Comorbidity Index; CHF: congestive heart failure; MI:
| Subgroup                  | OR          | No. of studies | $I^2$ (%) | $P_{(heterogeneity)}$ |
|--------------------------|-------------|----------------|-----------|----------------------|
|                          | (95% CI)    |                |           |                      |
| Study type               |             |                |           |                      |
| case-control             | 1.15 (1.03, 1.29) | 3              | 96        | <0.00                |
| cohort                   | 1.19 (1.11, 1.27) | 3              | 74        | 0.02                 |
| Study region             |             |                |           |                      |
| Asia                     | 1.26 (1.22, 1.30) | 3              | 11        | 0.33                 |
| North America            | 1.08 (0.95, 1.23) | 2              | 58        | 0.12                 |
| Europe                   | 1.13 (1.11, 1.15) | 1              | NA        | NA                   |
| Female percentage        |             |                |           |                      |
| ≥50%                     | 1.19 (1.13, 1.26) | 5              | 93        | <0.00                |
| <50%                     | 0.98 (0.82, 1.17) | 1              | NA        | NA                   |
| Participants             |             |                |           |                      |
| ≥200 thousand            | 1.13 (1.11, 1.15) | 2              | 0         | 1.00                 |
| <200 thousand            | 1.22 (1.14, 1.30) | 4              | 70        | 0.02                 |
| Mean age                 |             |                |           |                      |
| ≥60 years                | 1.16 (1.09, 1.24) | 2              | 70        | 0.07                 |
| <60 years                | 1.18 (1.08, 1.29) | 4              | 94        | <0.00                |
| Quality of study*        |             |                |           |                      |
| high                     | 1.18 (1.07, 1.30) | 2              | 81        | 0.02                 |
| moderate                 | 1.17 (1.07, 1.28) | 4              | 92        | <0.00                |

*A total score of 4-6 was considered moderate quality, and 7-9 was deemed high quality.

Table 2: Subgroup analyses of risk of herpes zoster among statin users.
Flow chart of the meta-analysis of association between statin use and herpes zoster.

The related literatures were obtained from the database (n=249, pubmed=24, embase=172, web of science=50, cochrane=3).

173x170mm (300 x 300 DPI)
Forest plot of the meta-analysis of association between statin use and herpes zoster.

186x128mm (300 x 300 DPI)
Funnel plot of the meta-analysis of association between statin use and herpes zoster.

101x73mm (300 x 300 DPI)
Search strategies in Pubmed

#1. (((((((exp Herpes Zoster[Title/Abstract]) OR Herpesvirus 3, Human[Title/Abstract]) OR shingles[Title/Abstract]) OR zoster[Title/Abstract]) OR Varicellovirus[Title/Abstract]) OR varicellovir*[Title/Abstract]) OR ((hhv3[Title/Abstract] OR hhv-3[Title/Abstract])) OR "Herpes Zoster"[Mesh]))

#2. (((((((exp Hydroxymethylglutaryl-CoA Reductase Inhibitors[Title/Abstract]) OR hydroxymethylglutaryl-CoA reductase inhibitor*[Title/Abstract]) OR HMG CoA reductase inhibitor*[Title/Abstract]) OR statin*[Title/Abstract]) OR atorvastatin[Title/Abstract]) OR cerivastatin[Title/Abstract]) OR dalvastatin[Title/Abstract]) OR fluindostatin[Title/Abstract]) OR fluvastatin[Title/Abstract]) OR lovastatin[Title/Abstract]) OR pitavastatin[Title/Abstract]) OR pravastatin[Title/Abstract]) OR rosuvastatin[Title/Abstract]) OR simvastatin[Title/Abstract]) OR ((meglutol[Title/Abstract] OR mevinolin*[Title/Abstract] OR monacolin*[Title/Abstract] OR pravachol[Title/Abstract] OR lipex[Title/Abstract] OR lipitor[Title/Abstract] OR zocor[Title/Abstract] OR mevacor[Title/Abstract] OR lescol[Title/Abstract] OR baycol[Title/Abstract]))) OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors" [Pharmacological Action])

#3. #1 AND #2
Search strategies in Emabase

#1. 'herpes zoster'/exp OR 'varicella zoster virus':ab,ti OR shingles:ab,ti OR zoster:ab,ti OR (varicella NEAR/3 virus*):ab,ti OR varicellovirus:ab,ti OR varicellovir*:ab,ti OR 'hhv 3':ab,ti OR hhv3:ab,ti

#2. ('hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp OR 'hmg coa reductase inhibitor*':ab,ti OR 'hmg co a reductase inhibitor*':ab,ti OR statin*:ab,ti OR atorvastatin:ab,ti OR cerivastatin:ab,ti OR dalvastatin:ab,ti OR fluindostatin:ab,ti OR fluvastatin:ab,ti OR lovastatin:ab,ti OR pitavastatin:ab,ti OR pravastatin:ab,ti OR simvastatin:ab,ti OR rosuvastatin:ab,ti OR meglutol:ab,ti OR mevinolin*:ab,ti OR monacolin*:ab,ti OR pravachol:ab,ti OR lipex:ab,ti OR lipitor:ab,ti OR zocor:ab,ti OR mevacor:ab,ti OR lescol:ab,ti OR baycol:ab,ti)

#3. #1 AND #2

Search strategies in Web of Science

#1. TOPIC: ("Herpes Zoster") OR TOPIC: (Herpesvirus

3) OR TOPIC: (shingles) OR TOPIC: (zoster) OR TOPIC: (Varicellovirus) OR TOPIC: (varicellovir*) OR TOPIC: (hhv3) OR TOPIC: (hhv-3)

#2. TOPIC: ("Hydroxymethylglutaryl-CoA Reductase Inhibitors") OR TOPIC: ("hydroxymethylglutaryl-CoA reductase
inhibitor*") OR TOPIC:("HMG CoA reductase
inhibitor*") OR TOPIC: (statin*) OR TOPIC: (atorvastatin) OR TOPIC: (cerivastatin) OR TOPIC: (dalvastatin) OR TOPIC: (fluindostatin) OR TOPIC: (fluvastatin) OR TOPIC: (lovastatin) OR TOPIC: (pitavastatin) OR TOPIC: (pravastatin) OR TOPIC: (rosuvastatin) OR TOPIC: (simvastatin) OR TOPIC: (mevacepl) OR TOPIC: (mevinolin*) OR TOPIC: (monacolin*) OR TOPIC: (pravachol) OR TOPIC: (lipex) OR TOPIC: (lipitor) OR TOPIC: (zocor) OR TOPIC: (mevacor) OR TOPIC: (lescol) OR TOPIC: (baycol)

#3. #1 AND #2

Search strategies in Cochrane

#1. "herpes zoster":ti,ab,kw OR herpesvirus:ti,ab,kw OR shingles:ti,ab,kw OR zoster:ti,ab,kw OR varicellovirus:ti,ab,kw OR varicellovir*:ti,ab,kw OR hhv3:ti,ab,kw OR hhv-3:ti,ab,kw (Word variations have been searched)

#2. "Hydroxymethylglutaryl-CoA Reductase Inhibitors":ti,ab,kw OR "hydroxymethylglutaryl-CoA reductase inhibitor*":ti,ab,kw OR "HMG CoA reductase inhibitor*":ti,ab,kw OR statin*:ti,ab,kw OR atorvastatin:ti,ab,kw OR cerivastatin:ti,ab,kw OR dalvastatin:ti,ab,kw OR fluindostatin:ti,ab,kw OR fluvastatin:ti,ab,kw OR lovastatin:ti,ab,kw OR pitavastatin:ti,ab,kw OR "pravastatin":ti,ab,kw OR rosuvastatin:ti,ab,kw OR simvastatin:ti,ab,kw OR meglutol:ti,ab,kw OR mevinolin*:ti,ab,kw OR monacolin*:ti,ab,kw OR
pravachol:ti,ab,kw OR Lipex:ti,ab,kw OR lipitor:ti,ab,kw OR Zocor:ti,ab,kw
OR mevacor:ti,ab,kw OR lescol:ti,ab,kw OR baycol:ti,ab,kw (Word variations have been searched)

#3. #1 AND #2
| Matthews et al., 2016 | Kim et al., 2008 | Cirillo et al., 2014 | Chung et al., 2014 | Shen et al., 2014 |
|----------------------|------------------|---------------------|-------------------|-------------------|
| Is the case definition adequate/Representativeness of the exposed cohort |
| Representativeness of the cases/Selection of the non-exposed cohort |
| Selection of Controls/Ascertainment of exposure |
| Definition of Controls/Demonstration that outcome of interest was not present at start of study |
| Select the most important factor |
| Select any additional factor |
| Ascertainment of exposure/Assessment of outcome |
| Same method of ascertainment for cases and controls/Was follow-up long enough for outcomes to occur |
| Non-response rate/Adequacy of follow-up of cohorts |
## PRISMA 2009 Checklist

| Section/topic | # | Checklist item                                                                                                                                                                                                                                                                                                                                                       | Reported on page # |
|---------------|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| TITLE         |   |                                                                                                                                                                                                                                                                                                                                                                       |                   |
| Title         | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                                                                                                                                                                    |                   |
| ABSTRACT      |   |                                                                                                                                                                                                                                                                                                                                                                       |                   |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.                                               |                   |
| INTRODUCTION  |   |                                                                                                                                                                                                                                                                                                                                                                       |                   |
| Rationale     | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                                                                                                                                                                          |                   |
| Objectives    | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                                                                         |                   |
| METHODS       |   |                                                                                                                                                                                                                                                                                                                                                                       |                   |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                                                                                                                                  |                   |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                                                                                                |                   |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                                                         | 4-5               |
| Search        | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                                                                                                             |                   |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                                           |                   |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                                                                                                 |                   |
| Data items    | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                                                                                                                                                                  |                   |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                                                                                                               | 6-7               |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                                                                                                                                                                            |                   |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.                                                                                                                                                          |                   |
| Section/topic                      | #  | Checklist item                                                                 | Reported on page # |
|-----------------------------------|----|---------------------------------------------------------------------------------|-------------------|
| Risk of bias across studies      | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 7                 |
| Additional analyses              | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6-7               |
| **RESULTS**                      |    |                                                                                 |                   |
| Study selection                   | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 7                 |
| Study characteristics             | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 8                 |
| Risk of bias within studies       | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9                 |
| Results of individual studies     | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 8-9               |
| Synthesis of results              | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 8-9               |
| Risk of bias across studies       | 22 | Present results of any assessment of risk of bias across studies (see item 15). | 10                |
| Additional analysis               | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 9-10              |
| **DISCUSSION**                   |    |                                                                                 |                   |
| Summary of evidence               | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 10                |
| Limitations                       | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 12                |
| Conclusions                       | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13                |
| **FUNDING**                      |    |                                                                                 |                   |
| Funding                           | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 1                 |

*From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097*

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).