Association between statin use and risk of gallstone disease and cholecystectomy: A meta-analysis of 590,086 patients

Yu Chang [Equal first author, 1], **Hong-Min Lin** [Equal first author, 2], **Kuan-Yu Chi** [3], **Wan-Ying Lin** [3], **Tsung-Ching Chou** [Corresp. 1]

[1] National Cheng Kung University Hospital, Tainan, Taiwan, 台灣

[2] Chi-Mei Medical Center, Tainan, Taiwan, 台灣

[3] Taipei Medical University, Taipei, Taiwan

Corresponding Author: Tsung-Ching Chou
Email address: chou5182@gmail.com

Background Statins have been reported to reduce the risk of gallstone disease. However, the impacts of different durations of statin use on gallstone disease have not been clarified. The aim of this study is toperform a systematic review with meta-analysis to update and to elucidate the association between statin use and the risk of gallstone disease and cholecystectomy. **Methods** Medline, Embase and Cochrane Library were searched from the inception until August 2022 for relevant articles investigating the difference in the risk of gallstone disease between statin users and non-users (PROSPERO, ID: CRD42020182445). Meta-analyses were conducted using odds ratios (ORs) with corresponding 95% confidence intervals (CIs) to compare the risk of gallstone disease and cholecystectomy between statin user and nonusers.. **Results** Eight studies enrolling 590,086 patients were included. Overall, the use of statins was associated with a marginally significant lower risk of gallstone disease than nonusers (OR, 0.91; 95% CI, 0.82 to 1.00). Further subgroup analysis showed that short-term users, medium-term users, and long-term users were associated with a significantly higher risk (OR, 1.18; 95% CI, 1.11 to 1.25), comparable risk (OR, 0.93; 95% CI, 0.83 to 1.04), and significantly lower risk of gallstone diseases (OR, 0.78; 95% CI, 0.68 to 0.90) respectively, compared to nonusers. **Conclusions** Patients with medium-term or long-term use of statins without discontinuation are at a lower risk of gallstone disease or cholecystectomy.

1   **Association between statin use and risk of gallstone disease and cholecystectomy: A meta-**

2   **analysis of 590,086 patients**

3   Yu Chang[1†], M.D, Hong-Min, Lin [2†], M.D, Kuan-Yu Chi[3,4], M.D, Wan-Ying, Lin[5], M.D, Tsung-

4   Ching Chou[1*], M.D

5   [1]Departement of Surgery, National Cheng Kung University Hospital, National Cheng Kung

6   University, Tainan, Taiwan

7   [2] Department of Family Medicine, Chi-Mei Medical Center, Tainan, Taiwan

8   [3]Departement of Education, Center for Evidence-Based Medicine, Taipei Medical University

9   Hospital, Taipei, Taiwan

10   [4]Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan

11   [5]Department of Family Medicine, Taipei Medical University Hospital, Taipei, Taiwan

12   †Authors equally contributed to the manuscript

13   ***Corresponding author**

14   Tsung-Ching Chou

15   Attending Doctor, Department of Surgery, National Cheng Kung University Hospital

16   Tel: 886-6-2353535, Ext 3440

17   E-Mail: chou5182@gmail.com

Abstract

Background

Statins have been reported to reduce the risk of gallstone disease. However, the impacts of

different durations of statin use on gallstone disease have not been clarified. The aim of this

study is to perform a systematic review with meta-analysis to update and to elucidate the

association between statin use and the risk of gallstone disease and cholecystectomy.

Methods

Medline, Embase and Cochrane Library were searched from the inception until August 2022 for

relevant articles investigating the difference in the risk of gallstone disease between statin users

and non-users (PROSPERO, ID: CRD42020182445). Meta-analyses were conducted using odds

ratios (ORs) with corresponding 95% confidence intervals (CIs) to compare the risk of gallstone

disease and cholecystectomy between statin user and nonusers..

Results

Eight studies enrolling 590,086 patients were included. Overall, the use of statins was associated

with a marginally significant lower risk of gallstone disease than nonusers (OR, 0.91; 95% CI,

0.82 to 1.00). Further subgroup analysis showed that short-term users, medium-term users, and

long-term users were associated with a significantly higher risk (OR, 1.18; 95% CI, 1.11 to

1.25), comparable risk (OR, 0.93; 95% CI, 0.83 to 1.04), and significantly lower risk of gallstone

diseases (OR, 0.78; 95% CI, 0.68 to 0.90) respectively, compared to nonusers.

Conclusions

Patients with medium-term or long-term use of statins without discontinuation are at a lower risk

47   of gallstone disease or cholecystectomy.

48

49

50   **Introduction**

51   Gallstone is one of the most common indications for hospitalization in developed countries[1]. The

52   prevalence of gallstone in the western population is between 10-30%[2]. Regarding the treatment

53   of symptomatic cholelithiasis, cholecystectomy is an optimal management with its surgical

54   volume reaching up to 70,000 in the United States in 2008[1,3]. Gallstones primarily fall into two

55   compositions, cholesterol and pigment stones, with the former accounting for 80-90% of all

56   cases[2]. Nowadays, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors,

57   namely statins, are widely used for the treatment and prevention of cardiovascular disease due to

58   their well-established therapeutic effects on low-density lipoprotein cholesterol (LDL-C), which

59   is one of the major risk factors for atherosclerosis and coronary heart disease[4]. In addition to the

60   effects on cardiovascular system, statins significantly decrease cholesterol biosynthesis, which

61   may potentially reduce cholesterol concentration in the biliary system[5]. Although it has been

62   proven in animal studies that statin may alter biliary lipid composition, thereby reducing the risk

63   of gallstone development[6,7], in human studies it differed widely in the outcomes. Some studies

64   ascertained statins' efficacy of decreasing cholesterol concentration in bile or dissolving

65   gallstones[8-11], whereas others found little effect of statins on bile composition[12-14]. The latest

66   meta-analysis[15] in 2015 concluded that statin users have lower risk of gallstone disease.

67   However, considerable heterogeneity has remained unexplored, and the impacts of different

68   durations and discontinuation of statin use on gallstone varied in the literature. For example,

69   while Erichsen et al. [16] reported lower risk of gallstone disease among long-term user, more

70   recently, Biétry et al.[17] reported comparable risk of gallstone disease among long-term user and

71   nonusers. Moreover, the definition of statin current user or former users was not consistent

72   across published studies. Hence, we sought to perform a meta-analysis to integrate the available

73   and relevant literature and determine the association between statin use and risk of gallstone

74   disease and cholecystectomy.

75

76   **Methods**

77   We conducted the present systematic review and meta-analysis following Cochrane Handbook

78   for Systematic Reviews and Interventions[18] and reported the results based on the Preferred

79   Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analysis Of Observational

80   Studies in Epidemiology guidelines (**Supplemental Method 1 and 2**). Electronic databases of

81   Medline, Embase, and Cochrane library were searched from the inception until August 2022,

82   encompassing all languages. This study was registered on PROSPERO (ID: CRD42020182445).

83   Before the registration, we completed the formal screening of search results against eligibility

84   criteria, since PROSPERO accepts registration for reviews that have not started data extraction.

85   Two investigators (Y.C and K.Y.C) independently conducted the search to determine relevant

86   studies to be included, and any discrepancy was addressed by reaching a consensus or by

87   consulting a senior reviewer (T.C.C). Search details are presented in the **Supplemental Method**

88   **3**.

89   *Eligibility criteria*

90   Articles with the following criteria were included: (1) Randomized controlled trials, prospective

91   studies, retrospective studies and case-control studies; (2) studies involving human adults

92   without history of gallstone disease or cholecystectomy as participants; (3) studies reporting

93 clinical outcome as with/without diagnosis of gallstone disease or record of cholecystectomy.

94 Studies not investigating the use of statins were excluded. In case of duplicate studies with an

95 accumulated number of patients or increased durations of follow-up, only the most complete

96 reports were included

97 ***Data extraction***

98 Two investigators (Y.C and K.Y.C) independently extracted relevant information from tables or

99 results of eligible articles. Extracted data included first author name, publication year, country

100 where the study was conducted, follow-up durations, number of participants, sex, age range,

101 underlying diseases, and method used to identify cases. Additionally, we obtained adjusted odds

102 ratio (OR) and standard error (SE) from each study. For studies that reported outcomes by

103 relative risk (RR), since the extracted RR and SE were adjusted, the formula[19] for the conversion

104 between RR and OR may be inappropriate. Therefore, we regarded the adjusted RR as OR since

105 most of the included studies have incidence of outcome less than 10% and all ORs converted

106 from RRs were between 0.5 and 2.5, correction may not be desirable[20].

107 ***Quality assessment***

108 Two investigators (Y.C and H.M.L) independently completed a critical appraisal of included

109 literature by using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I)

110 tool[21] for retrospective cohorts and National Heart, Lung, and Blood Institute tool for case-

111 control studies. Any item on which assessors did not reach a consensus was addressed through

112 discussion with third investigator (T.C.C).

113 ***Statistical analysis***

114 Meta-analysis was conducted using R software with the "metafor" package[22] (**Supplemental**

115   **Method 4**). Regarding the risk of gallstone disease, we used the inverse variance (IV) method to

116   pool the odds ratio obtained from each study regarding risk of gallstone disease among statin

117   users and non-users. The restricted maximum likelihood (REML)[23] method was exploited as a

118   heterogeneity estimator for conducting random-effects meta-analyses given that the between-trial

119   variance was inevitable. P values <0.05 were considered statistically significant. Heterogeneity

120   was assessed using I^2 statistics proposed by Higgins and Thompson[24], with estimated values of

121    $I^2 < 25\%$, $25\% < I^2 < 50\%$, and $I^2 \geq 50\%$ indicating low, moderate, and high heterogeneity,

122   respectively. We aimed to explore the statistical heterogeneity of our meta-analysis by

123   performing subgroup analysis based on the durations of statin use (long-term, medium-term and

124   short-term) and current or former statin users.

125   **Results**

126   *Study selection*

127   Our search strategy identified 1007 references from Medline, Embase, and Cochrane library.

128   After title and abstract screening, we excluded duplicates (n= 49) and irrelevant references (n=

129   942) and retrieved 16 full texts for further review. Eventually, 6 case-control studies[16-16,17,26-29]

130   and 2 retrospective cohort studies[25,30] met the eligibility criteria for qualitative and quantitative

131   synthesis. *Figure 1* shows the flowchart of study selection.

132   *Characteristic of included studies and patients (Table 1)*

133   Among 8 studies[16,17,25-30] enrolling 590,086 participants from 1994 to 2012, 5 studies[17,25,26,228,29]

134   recruited patients who underwent cholecystectomy due to gallstone diseases, and other 3

135   studies[16,27,30] included patients with the diagnosis of gallstone diseases. Of note, 5 studies[16,17,26-28]

136   specifically categorized patients into statin current, past, or nonusers, and the other 3

137   studies[25,29,30] referred to statin users as any statin prescription prior to the index date, defined as

138   the first-time diagnosis of gallstone diseases or the date of cholecystectomy in patients without

139   the record of cholelithiasis. Detailed patient characteristics were summarized in **Supplemental**

140   **Table 1 and 2**. Regarding the durations of statin use, 3 of the included studies[16,17,28] classified

141   the durations of statin use based on the numbers of prescription prior to the index date

142   **(Supplemental Table 3 and Table 4)**.

143   ***Quality assessment of included studies***

144   **Supplemental Table 5** demonstrated the summary of quality assessment for case-control studies

145   using the National Heart, Lung, and Blood Institute tool, and the overall quality was good in 3

146   studies and the other 3 were fair. **Supplemental Table 6** demonstrated the risk of bias

147   assessment using ROBINS-I tool for two retrospective cohort studies, which were evaluated as

148   moderate risk of bias resulted from bias due to confounding.

149   ***Risk of cholelithiasis and cholecystectomy***

150   Overall, the pooled result of 8 studies[16,17,25-30] demonstrated that the use of statins was associated

151   with a marginally significant lower risk of gallstone disease than nonusers, however, with

152   substantial heterogeneity (OR, 0.91; 95% CI, 0.82 to 1.00, I^2 =86%; ***Figure 2***).

153   ***Durations of statin use***

154   To explore the source of heterogeneity, we performed subgroup analysis according to the

155   durations of statin use in three studies[16,17,28] that exclusively classified the durations based on the

156   number of prescriptions prior to the index date (short-term,1-4; medium, 5-19; long-term, over

157   20). Notably, our subgroup analysis seemed to show a dose-response tendency (***Figure 3)***. Shor-

158   term use of statins is associated with higher risk of gallstone disease in both current (OR, 1.16;

159   95% CI, 1.07 to 1.26, $I^2 = 0$ %; with gallstone disease: 804 patients; without gallstone disease:

160   4430 patients) and former users (OR, 1.20; 95% CI, 1.10 to 1.30, $I^2 = 35$ %; with gallstone

161   disease: 717 patients; without gallstone disease: 3469 patients). Medium-term current statin user

162   had significant lower risk of gallstone disease compared to nonusers (OR, 0.86; 95% CI, 0.81 to

163   0.91, $I^2 = 15$ %; with gallstone disease: 1737 patients; without gallstone disease: 10923 patients)

164   and former users had comparable risk of gallstone disease compared to nonusers (OR, 1.05; 95%

165   CI, 0.91 to 1.21, $I^2 = 50$ %; with gallstone disease: 587 patients; without gallstone disease: 3259

166   patients). Long-term use of statin significantly reduced the risk of gallstone disease in current

167   users (OR, 0.73; 95% CI, 0.62 to 0.87, $I^2 = 82$ %; with gallstone disease: 1451 patients; without

168   gallstone disease: 9096 patients) but former users had comparable risk of gallstone disease

169   compared to nonusers (OR, 0.87; 95% CI, 0.72 to 1.05, $I^2 = 0$ %; with gallstone disease: 204

170   patients; without gallstone disease: 1327 patients).

171   Additionally, the pooled analysis of 4 studies[16,25,27,30] involving statin-users over 1-year period

172   showed a significantly lower risk of gallstone diseases (OR, 0.83; 95% CI, 0.77 to 0.89; $I^2 = 4$%;

173   *Figure 4*).

174   **Discussion**

175   ***Risk of cholecystectomy and cholelithiasis***

176   Statins are one of the most common prescribed regimens in the treatment and prevention of

177   cardiovascular disease[31]. In addition to lowering the risk of cardiovascular disease, some studies

178   have demonstrated that statins may reduce the risk of urolithiasis[32,33]. Notably, our study

179   revealed that statin users had marginally significant reduced risk of gallstone disease, compared

180   to non-users, however, with high statistical heterogeneity ($I^2 = 71$%).

181   One of the sources of heterogeneity would arise from the differences in demographics among

182   included studies. For example, there were wide variation in prevalence of diabetes, ischemic

183   heart diseases, and cerebrovascular diseases among included studies. Moreover, baseline

184   characteristics that may be associated with gallstone disease such as hyperlipidemia, estrogen

185   exposure or hormone therapy were only reported in two studies. On the other hand, we acquired

186   adjusted ORs from included studies and pooled in meta-analysis, however, the variables adjusted

187   for were not consistent in each study, which would contribute to the statistical heterogeneity.

188   Most of the included studies defined case as "cholecystectomy required". The use of statin may

189   not only impact the formation of gallstone but the symptom severity of gallstone disease. For

190   instance, Suuronen et al. found a decreased number of all cholecystectomies but increased

191   number of laparoscopic cholecystectomy (LC) with statin use in their population-based study[34].

192   They described one of the reasons may be an increased incidence of mild symptomatic gallstones

193   leading to LC. The utilization of different approaches may reflect the severity of the disease,

194   however, none of included studies investigated the difference between open and laparoscopic

195   cholecystectomy.

196   ***Gallstone disease risk of statin users with different durations of use***

197   Our results demonstrated that there was a marginally significant reduction in the risk of

198   developing gallstone disease among statin-ever users. The subgroup analysis showed a dose-

199   response relationship between the number of prescription and the risk of gallstone diseases, and,

200   of note, the protective effect of stain was only observed in medium and long-term current users.

201   However, this result had to be interpreted with caution since the durations of statin use was

202   solely based on the prescription of medication in medical records. Paucity of detailed dosage of

203   statin prescription and information for drug compliance may hindered the accuracy of statin

204   exposure. Moreover, the cut-off time selected for the definition of current and former users

205   varied from 90 days to 180 days representing an obvious source of conceptual heterogeneity.

206   As a matter of fact, long-term statin users only accounted for 15% of all statin users in our

207   analysis. We postulated that the underlying reason for such small proportion may be associated

208   with either discontinuation of statins or low adherence to medications. Although statins are one

209   of the most effective medications for the secondary prevention of cardiovascular diseases, non-

210   compliance and discontinuation with this medication are common problems[35-37]. Although

211   patient-perceived side effect is the most common reason for statin discontinuation[38], the

212   incidence of statins' most common side effect, namely myopathy, is only estimated to be around

213   0.01%[39]. Of note, those not adhering to statins, mostly due to self-perceived stable disease

214   condition[40], may experience relapsing dyslipidemia following statin discontinuation leading to

215   worsening cardiovascular and survival outcomes[41,42].

216   Consequently, we propose that the recurrence of dyslipidemia may be responsible for neutral and

217   detrimental effects on gallstone formation in medium- and short-term users, respectively.

218   ***Compare to previous synthesis***

219   In our study, we included three more studies[17,27,30] compared with the previous one. In

220   accordance with the study by Kan et al.[15], our results demonstrated patients with medium-term

221   use and long-term use of statin users conferred to lower risk of gallstone disease. However, we

222   addressed several concerns that were not well-elucidated in previous study. First, we clarified the

223   impacts of statin discontinuation on gallstone disease. Second, we excluded cross-sectional study

224   in our meta-analysis since this type of study is estimating the prevalence but incidence[43]. The

225   cross-sectional study by Caroli-Bosc[44] in the previous meta-analysis might not contribute to

226   statistical heterogeneity, however, conceptually, it brings between-study variance. Third,

227   methodologically, we performed our meta-analysis through a more robust heterogeneity

228   estimator based on the latest simulation study[45].

229   *Limitation*

230   The findings of our meta-analysis must be interpreted within the context of the study limitations.

231   First, we included case-control studies and retrospective cohort studies, which induced a

232   potential bias due to the confounding that was generally not well-controlled. Second, we

233   investigated the protective effect of statin on gallstone development, however, the definition of

234   statin use, and gallstone disease were not consistent in each study. Third, baseline characteristics

235   that may be associated with gallstone formation such as hyperlipidemia, estrogen exposure or

236   hormone therapy were not reported in several studies, which hindered the accuracy of our

237   findings. Last but not least, healthy user and adherer effect are two easily overlooked sources of

238   bias, especially in observational studies[46]. Patients who are willing to take and adhere to statins

239   are more likely to be engaged with healthy behaviors, contributing to the protective effects of

240   statins. Unfortunately, It is difficult to adjust these healthier behaviors through observational

241   design, leading to unmeasured confounding bias.

242   **Conclusions**

243   Based on our meta-analysis, long-term and medium-term use of statins without discontinuation

244   lower the risk of gallstone disease or cholecystectomy. Nonetheless, given the observational

245   nature of the included studies, we propose that further prospective studies should be undertaken

246   to overcome the aforementioned limitations.

247   **Acknowledgments**

248   Not applicable

249   **Reference**

250   1.   Beckingham IJ. ABC of diseases of liver, pancreas, and biliary system. Gallstone disease.
251   Bmj. 2001;322(7278):91-94.
252   2.   Marschall HU, Einarsson C. Gallstone disease. J Intern Med. 2007;261(6):529-542.
253   3.   Lammert F, Miquel JF. Gallstone disease: from genes to evidence-based therapy. J
254   Hepatol. 2008;48 Suppl 1:S124-135.
255   4.   Awad K, Serban MC, Penson P, et al. Effects of morning vs evening statin administration
256   on lipid profile: A systematic review and meta-analysis. J Clin Lipidol. 2017;11(4):972-
257   985.e979.
258   5.   Kallien G, Lange K, Stange EF, Scheibner J. The pravastatin-induced decrease of biliary
259   cholesterol secretion is not directly related to an inhibition of cholesterol synthesis in
260   humans. Hepatology. 1999;30(1):14-20.
261   6.   Davis KG, Wertin TM, Schriver JP. The Use of Simvastatin for the Prevention of
262   Gallstones in the Lithogenic Prairie Dog Model. Obesity Surgery. 2003;13(6):865-868.
263   7.   Abedin MZ, Narins SC, Park EH, Smith PR, Kirkwood KS. Lovastatin alters biliary lipid
264   composition and dissolves gallstones: A long-term study in prairie dogs. Digestive Diseases
265   and Sciences. 2002;47(10):2192-2210.
266   8.   Porsch-Ozçürümez M, Hardt PD, Schnell-Kretschmer H, et al. Effects of fluvastatin on
267   biliary lipids in subjects with an elevated cholesterol saturation index. European journal of
268   clinical pharmacology. 2001;56(12):873-879.
269   9.   Smith JL, Roach PD, Wittenberg LN, et al. Effects of simvastatin on hepatic cholesterol
270   metabolism, bile lithogenicity and bile acid hydrophobicity in patients with gallstones.
271   Journal of Gastroenterology and Hepatology (Australia). 2000;15(8):871-879.
272   10.   Chapman BA, Burt MJ, Chisholm RJ, Allan RB, Yeo KHJ, Ross AG. Dissolution of
273   gallstones with simvastatin, an HMG CoA reductase inhibitor. Digestive Diseases and
274   Sciences. 1998;43(2):349-353.
275   11.   Wilson IR, Hurrell MA, Pattinson NR, Chapman BA. The effect of simvastatin and
276   bezafibrate on bile composition and gall-bladder emptying in female non-insulin-dependent
277   diabetics. Journal of Gastroenterology and Hepatology (Australia). 1994;9(5):447-451.
278   12.   Miettinen TE, Kiviluoto T, Taavitsainen M, Vuoristo M, Miettinen TA. Cholesterol
279   metabolism and serum and biliary noncholesterol sterols in gallstone patients during
280   simvastatin and ursodeoxycholic acid treatments. Hepatology. 1998;27(3):649-655.
281   13.   Smit JW, van Erpecum KJ, Renooij W, et al. The effects of the 3-hydroxy, 3-
282   methylglutaryl coenzyme A reductase inhibitor pravastatin on bile composition and
283   nucleation of cholesterol crystals in cholesterol gallstone disease. Hepatology.
284   1995;21(6):1523-1529.

285   14.   Sharma BC, Agarwal DK, Baijal SS, Saraswat VA. Pravastatin has no effect on bile lipid
286   composition, nucleation time, and gallbladder motility in persons with normal levels of
287   cholesterol. Journal of Clinical Gastroenterol. 1997;25(2):433-436.
288   15. Kan HP, Guo Wb, Tan YF, Zhou J, Liu CD, Huang YQ. Statin use and risk of gallstone
289   disease: A meta-analysis. Hepatology Research. 2015;45(9):942-948.
290   16. Erichsen R, Frøslev T, Lash TL, Pedersen L, Sørensen HT. Long-term statin use and the risk
291   of gallstone disease: A population-based case-control study. American Journal of
292   Epidemiology. 2011;173(2):162-170.
293   17. Biétry FA, Reich O, Schwenkglenks M, Meier CR. Statin use and risk of cholecystectomy–
294   A case-control analysis using Swiss claims data. Expert Opinion on Drug Safety.
295   2016;15(12):1577-1582.
296   18. Julian Higgins JT, Jacqueline Chandler, Miranda Cumpston, Tianjing Li, Matthew Page,
297   Vivian Welch. Cochrane Handbook for Systematic Reviews of Interventions version 6.0.
298   In:2019.
299   19. Grant RL. Converting an odds ratio to a range of plausible relative risks for better
300   communication of research findings. Bmj. 2014;348:f7450.
301   20. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort
302   studies of common outcomes. Jama. 1998;280(19):1690-1691.
303   21. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-
304   randomised studies of interventions. BMJ. 2016;355:i4919-i4919.
305   22. Viechtbauer W. Conducting Meta-Analyses inRwith themetaforPackage. Journal of
306   Statistical Software. 2010;36(3).
307   23.   Harville DA. Maximum Likelihood Approaches to Variance Component Estimation and to
308   Related Problems. Journal of the American Statistical Association. 1977;72(358).
309   24. Higgins JPT. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-560.
310   25. Tsai C, Leitzmann MF, Willett WC, Giovannucci EL. Statin Use and the Risk of
311   Cholecystectomy in Women. Gastroenterology. 2009;136(5):1593-1600.
312   26. Merzon E, Weiss NS, Lustman AJ, Elhayani A, Dresner J, Vinker S. Statin administration
313   and risk of cholecystectomy: A population-based case-control study. Expert Opinion on Drug
314   Safety. 2010;9(4):539-543.
315   27. González-Pérez A, García Rodríguez LA. Gallbladder disease in the general population:
316   Association with cardiovascular morbidity and therapy. Pharmacoepidemiology and Drug
317   Safety. 2007;16(5):524-531.
318   28. Bodmer M, Brauchli YB, Krähenbühl S, Jick SS, Meier CR. Statin use and risk of gallstone
319   disease followed by cholecystectomy. JAMA - Journal of the American Medical Association.
320   2009;302(18):2001-2007.
321   29. Chiu HF, Chen CC, Kuo HW, Lee IM, Wu TN, Yang CY. Statin use and the risk of
322   gallstone disease: A population-based casecontrol study. Expert Opinion on Drug Safety.
323   2012;11(3):369-374.

324 30.   Martin D, Schmidt R, Mortensen EM, Mansi I. Association of Statin Therapy and Risks
325   of Cholelithiasis, Biliary Tract Diseases, and Gallbladder Procedures: Retrospective Cohort
326   Analysis of a US Population. Annals of Pharmacotherapy. 2016;50(3):161-171.
327 31. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for Prevention of Cardiovascular
328   Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services
329   Task Force. Jama. 2016;316(19):2008-2024.
330 32. Cohen AJ, Adamsky MA, Nottingham CU, et al. Impact of Statin Intake on Kidney Stone
331   Formation. Urology. 2019;124:57-61.
332 33. Sur RL, Masterson JH, Palazzi KL, et al. Impact of statins on nephrolithiasis in
333   hyperlipidemic patients: a 10-year review of an equal access health care system. Clin
334   Nephrol. 2013;79(5):351-355.
335 34. Suuronen S, Niskanen L, Paajanen P, Paajanen H. Declining cholecystectomy rate during
336   the era of statin use in Finland: a population-based cohort study between 1995 and 2009.
337   Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the
338   Scandinavian Surgical Society. 2013;102(3):158-163.
339 35. Navar AM, Roe MT, White JA, et al. Medication discontinuation in the IMPROVE IT trial.
340   Circ Cardiovasc Qual Outcomes 2019;12(1): e005041. 6.
341 36. Toth PP, Granowitz C, Hull M, Anderson A, Philip S. Long-term statin persistence is poor
342   among high-risk patients with dyslipidemia: a real-world administrative claims analysis.
343   Lipids Health Dis 2019;18(1):175.
344 37. Wei L, Wang J, Tompson P, Struthers S, MacDonald TM. Adherence to statin treatment
345   and readmission of patients after myocardial infarction: a six year follow up study. Heart.
346   2002;88(3):229–33
347 38. Bradley CK, Wang TY, Li S, Robinson JG, Roger VL, Goldberg AC, Virani SS, Louie MJ,
348   Lee LV, Peterson ED, Navar AM. Patient-Reported Reasons for Declining or Discontinuing
349   Statin Therapy: Insights From the PALM Registry. J Am Heart Assoc. 2019 Apr 2;8(7)
350 39. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA. 2003 Apr
351   2;289(13):1681-90. doi: 10.1001/jama.289.13.1681.
352 40. Kamal-Bahl SJ, Burke T, Watson D, Wentworth C. Discontinuation of lipid modifying
353   drugs among commercially insured United States patients in recent clinical practice. Am J
354   Cardiol. 2007 Feb 15;99(4):530-4.
355 41. Daskalopoulou SS, Delaney JA, Filion KB, et al. Discontinuation of statin therapy following
356   an acute myocardial infarction: a population-based study. Eur Heart J 2008; Jul 29
357 42. Rea F, Biffi A, Ronco R, Franchi M, Cammarota S, Citarella A, Conti V, Filippelli A,
358   Sellitto C, Corrao G. Cardiovascular Outcomes and Mortality Associated With Discontinuing
359   Statins in Older Patients Receiving Polypharmacy. JAMA Netw Open. 2021 Jun 1;4(6)
360 43. Sedgwick P. Cross sectional studies: advantages and disadvantages BMJ 2014; 348 :g2276
361 44. Caroli-Bosc FX, Le Gall P, Pugliese P, et al. Role of fibrates and HMG-CoA reductase
362   inhibitors in gallstone formation: epidemiological study in an unselected population.
363   Digestive Diseases & Sciences.46(3):540-544.

364   45. Langan D, Higgins JPT, Jackson D, et al. A comparison of heterogeneity variance estimators
365   in simulated random-effects meta-analyses. Res Synth Methods. 2019;10(1):83-98.
366

367   46. hrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational
368   studies of preventive interventions: a primer for physicians. J Gen Intern Med. 2011
369   May;26(5):546-50.
370

371

372

373

374

375

376

377

378

379

380

Characteristics of included studies

Characteristics of included studies

Table 1 Characteristics of included studies

Study, year	Study type	Country	Inclusion period	Match method	Exclusion criteria	Case definition	Statin use
Biétry 2016[23]	CC	Switzerland	2008~2014	1:4 matched on age, sex, and index date	Cancer or HIV	Cholecystectomy only	Prior to index date†, Current user: last prescription <180 days Former user: last prescription >180 days
Bodmer 2009[19]	CC	UK	1994~2008	1:4 matched on age, sex, and index date	Alcoholism, drug abuse, cancer or HIV	First time diagnosed gallstone disease followed by cholecystectomy in 2 years; or cholecystectomy only	Prior to index date, Current user: last prescription <90 days Former user: last prescription >90 days
Chiu 2012[21]	CC	Taiwan	1996~2009	1:1 matched on age, sex, and index date	Cancer	First time diagnosed gallstone disease followed by cholecystectomy in 2 years; or cholecystectomy only	Any prescription prior to index date
Erichsen 2010[17]	CC	Denmark	1996~2008	1:10 matched on age, sex	Preexisting gallstone disease or liver, bile duct or pancreatic cancer	Diagnosis of gallstone, cholecystitis or a record gallbladder surgery (cholecystectomy or drainage)	Prior to index date, Current user: last prescription <90 days; Former user: last prescription >90 days
González-Pérez 2007[18]	CC	UK	1996~1996	1:4 matched on age and sex	Preexisting gallstone disease or cancer	Symptomatic gallstone	Prior to index date, Current user: last prescription <30 days;

							Former user: last prescription >30 days
Merzon 2010[16]	CC	Israel	2003~2006	1:4 matched on age and sex	N/A	Cholecystectomy due to gallstone disease	Prior to index date, Last prescription <180 days prior to index date
Martin 2015[24]	RC	US	2003~2012	1:1 propensity matched	History of burn, trauma, statin use <90 days, or starting statin use after baseline period	Diagnosis of cholelithiasis	Statin use lasting over 90 days prior to index date
Tsai 2009[15]	RC and PC	US	1994~2000	N/A	Prior cholecystectomy or gallstone disease or cancer	Self-reported cholecystectomy	Prior to index date, Current user: self-reported current use from inception to 2000, Former user: no present use in 2000

CC, Case-control study, RC, retrospective cohort study, NA, not applicable

3
4
5
6
7
8
9

Figure 1

PRISMA flow diagram

The PRISMA flow diagram demonstrates a total of 1007 potential references were extracted initially and meta-analysis included 8 studies meeting the eligibility criteria.

PRISMA 2009 Flow Diagram

Identification

Records identified through database searching
(n=1007)

Screening

Records after duplicates removed
(n=958)

Records screened by titles
and abstracts
(n =958)

Records excluded
(n=942)

Eligibility

Full-text articles assessed for
eligibility
(n =16)

Full-text articles excluded, with
reasons
Review article (n=4)
Cross-sectional study (n=1)
No outcome reported (n=2)
No appropriate control group (n =1)

Included

Studies included in
qualitative synthesis
(n =8)

Studies included in
quantitative synthesis (meta-
analysis)
(n =8)

Figure 2

Risk of gallstone disease among statin users and nonusers

Forest plot for risk of gallstone disease among statin users versus nonusers. The size of squares is proportional to the weight of each study with the error bar showing the 95% CI. Red diamond represents the pooled estimate of OR with the 95% CI. CI, confidence interval; IV, inverse variance method; OR, odds ratio; SE, standard error of logOR; TE, logOR

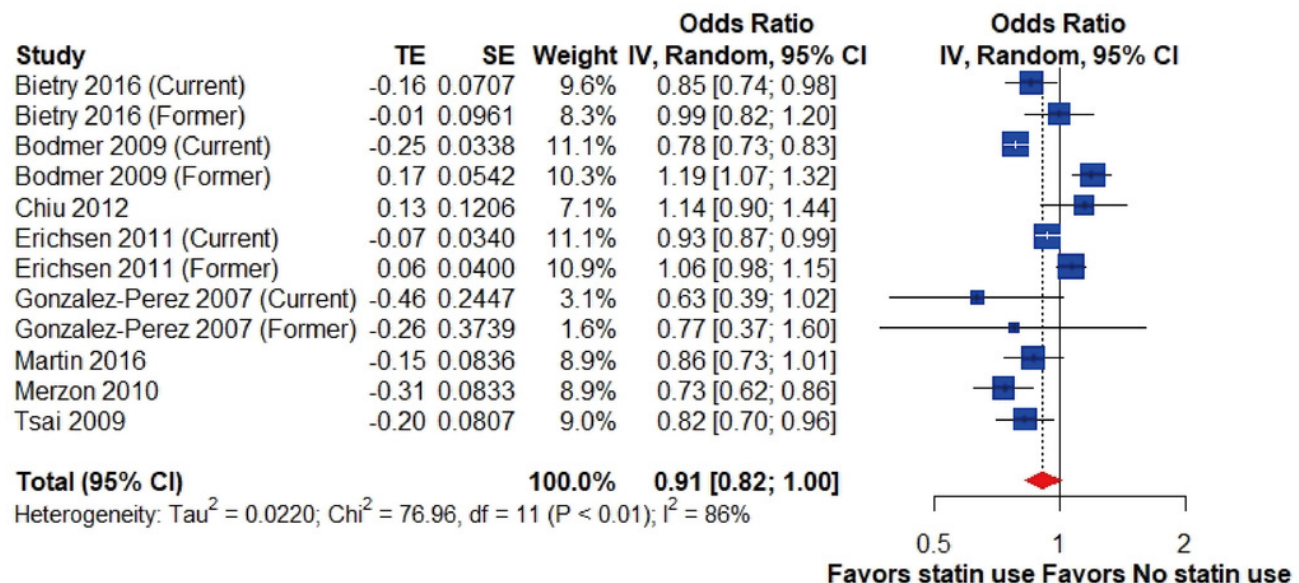
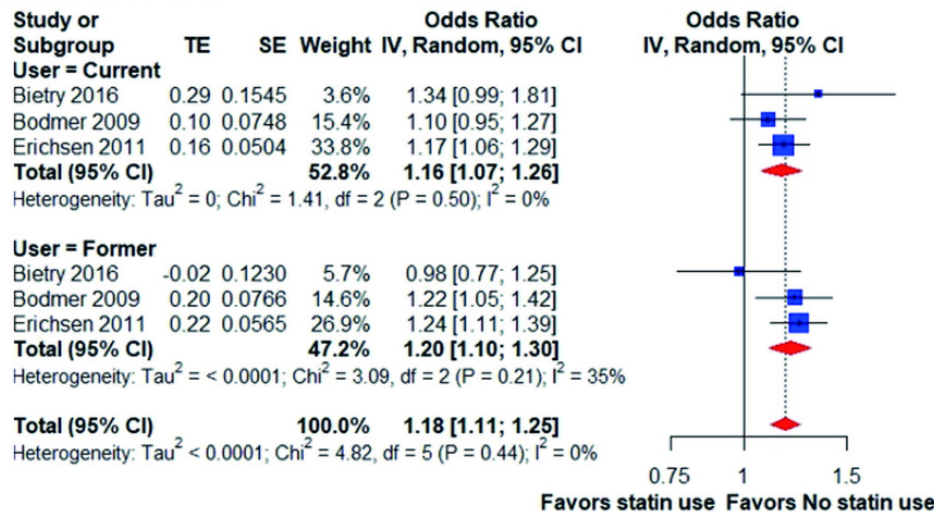
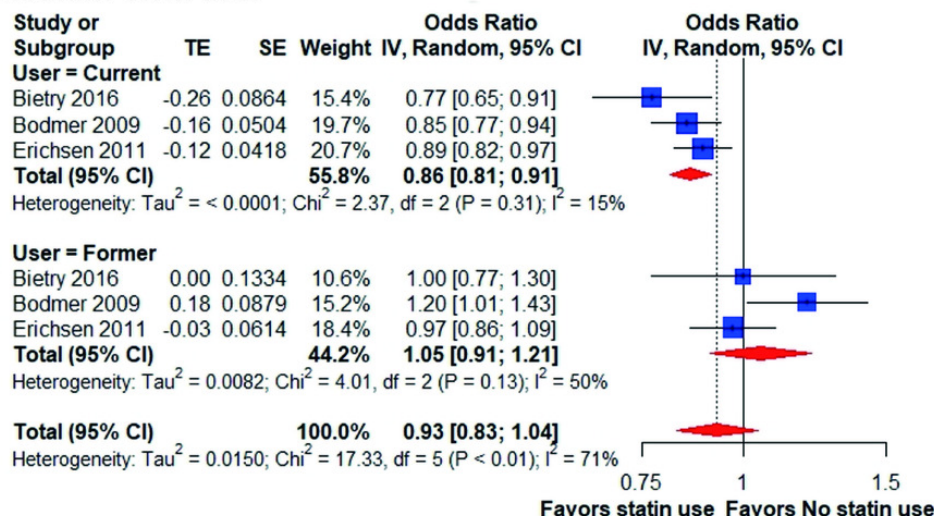



Figure 3

Risk of gallstone disease based on different duration of statin use

Forest plot for risk of gallstone disease among short-term, medium-term and long-term statin users compared to nonusers. Subgroup analysis was performed based on current and former users. The size of squares is proportional to the weight of each study with the error bar showing the 95% CI. Red diamond represents the pooled estimate of OR with the 95% CI. CI, confidence interval; IV, inverse variance method; OR, odds ratio; SE, standard error of logOR; TE, logOR

Short-term user

Medium-term user

Long-term user

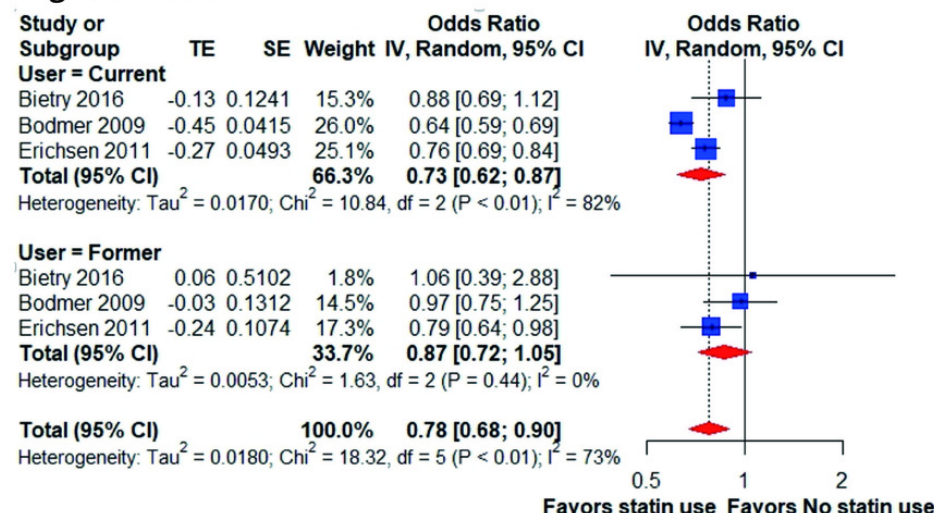



Figure 4

Risk of gallstone disease among long-term statin users (over one year)

Forest plot for risk of gallstone disease among long-term statin users versus nonusers. Subgroup analysis was performed based on current and former users. The size of squares is proportional to the weight of each study with the error bar showing the 95% CI. Red diamond represents the pooled estimate of OR with the 95% CI. CI, confidence interval; IV, inverse variance method; OR, odds ratio; SE, standard error of logOR; TE, logOR