Published in final edited form as:
Gastroenterology. 2009 May ; 136(5): 1593–1600. doi:10.1053/j.gastro.2009.01.042.

STATIN USE AND THE RISK OF CHOLECYSTECTOMY IN WOMEN

Chung-Jyi Tsai, M.D., Sc.D.[1,2], **Michael F. Leitzmann, M.D., Dr.P.H.**[4], **Walter C. Willett, M.D., Dr.P.H.**[2,3], and **Edward L. Giovannucci, M.D., Sc.D.**[2,3]

[1]Division of Digestive Diseases and Nutrition, University of Kentucky Medical Center, 800 Rose Street, Lexington, Kentucky 40536-0298

[2]Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115

[3]Departments of Nutrition and Epidemiology, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115

[4]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, 6120 Executive Blvd, Bethesda, MD 20892

Abstract

Background—Statins can reduce biliary cholesterol secretion independently of their ability to inhibit cholesterol synthesis. They also prevent formation of gallstones in animal studies, although the effect of statins on human gallstone disease has been controversial.

Methods—We examined the relationship between use of statins and the risk of cholecystectomy in a cohort of U.S. women. As part of the prospective Nurses' Health Study, participants biennially reported history of gallstone disease and whether they had undergone cholecystectomy. Women also reported lifetime use of statins retrospectively in 2000. We conducted a retrospective analysis of statin using data collected in 2000, to define use from 1994 forward, and a prospective analysis for general lipid-lowering drugs from 1994 to 2004.

Results—In the statin analysis we ascertained 2,479 cases of cholecystectomy during 305,197 person-years of follow-up. The multivariate relative risk for current statin users, compared with nonusers, was 0.82 (95% confidence interval, 0.70 to 0.96). In the analysis of general cholesterol-lowering drugs, we ascertained 3,420 cases of cholecystectomy during 511,411 person-years of follow-up. Compared with nonusers, the multivariate relative risk for current users of general cholesterol-lowering drugs, mostly statins in this cohort, was 0.88 (95% confidence interval, 0.79 to 0.98).

Conclusions—Statin use appears to reduce the risk of cholecystectomy in women.

Corresponding author: Chung-Jyi Tsai, M.D., Sc.D. Division of Digestive Diseases and Nutrition, University of Kentucky Medical Center, 800 Rose Street, Lexington, Kentucky 40536-0298. Fax: 859-257-8860 hpcjt@channing.harvard.edu.

The authors have no conflict of interest to disclose.

Keywords

statins; lipid-lowering drugs; HMG-CoA reductase inhibitors; gallstones; cholecystectomy; women

INTRODUCTION

Gallstone disease is a common abdominal condition in developed countries (1), and is a major cause of digestive morbidity leading to hospital admissions (2, 3). In the United States more than 800,000 cholecystectomies are performed each year. Among western populations the majority of the gallstones are cholesterol stones (4). Cholesterol gallstones have many causative factors, but biliary hypersecretion of cholesterol is an important determinant (4, 5).

Lipid-lowering drugs can have a significant effect on biliary lipid composition (6-8). Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzymatic step in cholesterol biosynthesis, commonly referred to as statins, have revolutionized the treatment of hypercholesterolemia and have been recently shown to exert beneficial effects beyond reducing serum cholesterol levels (9-12). Statins can reduce cholesterol secretion in the bile independent of inhibition of cholesterol synthesis in the cells (13). In addition, statins can beneficially raise plasma HDL cholesterol and decrease plasma triglycerides levels, and thereby may reduce the risk for gallstones (5, 14, 15). Statins decrease the cholesterol saturation index in duodenal bile in humans (16-19), and prevent formation of cholesterol gallstones in animal studies (20-22). These observations suggest that statins may reduce bile lithogenicity. However, studies of the effects of statins on gallstone disease in humans have been conflicting (7, 8, 23-25). The results of these clinical or experimental studies have been limited by small sample size or lack of long-term follow-up. Therefore, in a large cohort of US women, we examined the use of statins in relation to the occurrence of gallstone disease.

METHODS

Study Population

The Nurses' Health Study, an ongoing prospective cohort study in the United States, was initiated in 1976 when 121,700 female registered nurses, predominantly Caucasian, aged 30 to 55 years completed a mailed questionnaire on their medical history including gallstone disease and lifestyle characteristics. Every two years, follow-up questionnaires are sent to update information on exposures and to identify newly diagnosed illnesses. The follow-up rate for biennial questionnaires is near 90% or higher in each two-year follow-up cycle (26). Based on when the exposures of interest were queried, two follow-up periods were used for these analyses. Retrospective information on statin use was collected in 2000 to define exposure from 1994 forward, and the 2000 information on statin use was also used to examine incidence of cholecystectomy prospectively until 2004. Prospective analysis on use of general lipid-lowering drugs, mostly statins in this cohort, was conducted from 1994 to 2004. Each analysis began with all women who returned the questionnaire which first queried the exposure of interest. In each follow-up period, we excluded women who reported a prior cholecystectomy or a prior diagnosis of gallstone disease, women with a reported daily energy intake outside the range of 600-3500 Kcal/day, women with 70 or more blank food items on the dietary questionnaire, women with a diagnosis of cancer, and women with missing data on the primary exposures. After exclusions, the retrospective analysis of statin use included 53,611 women, and the prospective analysis of general lipid-lowering drugs use included 56,953 women. This study was approved by the institutional

review board on the use of human subjects in research of the Brigham and Women's Hospital and Harvard School of Public Health in Boston.

Assessment of Use of Statin and Other Cholesterol-Lowering Drugs

On the 2000 questionnaire participants were first asked to report separately whether they regularly used statin drugs. Statin users were asked to further specify duration of use in two-year categories up to six or more years. Current statin users were defined as those who reported current use on the 2000 questionnaire, with duration dating back to 1994 for those in the category of six or more years. No information was available on brand, type, or dose of medications used.

On biennial questionnaires participants in this prospective cohort were also asked whether they regularly used cholesterol-lowering drugs, including statins, bile acid sequestrants, fibrates, and nicotinic acids, during the previous 2 years. Statins were first introduced to the US market in 1987, and soon afterward their use surpassed that of other cholesterol-lowering drugs. Statins probably constituted the majority of the cholesterol-lowering drugs used in this cohort because they were the most commonly used type of cholesterol-lowering drug in the United States during this study period of time (27, 28). Indeed, responses to the 2000 questionnaire indicated that by that year approximately 93% of the cholesterol-lowering drugs used in this cohort were statins. Women were defined as current lipid-lowering drug users in any two-year questionnaire cycle they reported drug use, and they became past users when they no longer reported use on subsequent questionnaires. Duration of use was estimated by summing use across the 2-year periods encompassed by the biennial questionnaires.

Assessment of Dietary and Non-Dietary Variables

Dietary information was derived from a 131-item semi-quantitative food frequency questionnaire (SFFQ) (29). Participants were asked to indicate the frequency, on average, of consuming a typical serving size of selected foods during the previous year. There were nine options for respondents to choose from, ranging from never or less than once per month to six or more times per day. Nutrient scores were computed by multiplying the frequency of consumption of each unit of food from the SFFQ by the nutrient content of the specified portion according to food-composition tables from the Harvard Food Composition Database and U.S. Department of Agriculture supplemented with manufacturers' data (30). A full description of the SFFQ and the procedures used for calculating nutrient intake, as well as data on reproducibility and validity in this cohort, were reported previously (29). Validity of the dietary data was documented by comparisons with multiple-week dietary records corrected for within-person variation in diet. Participants also reported their body weight, cigarette smoking, use of medications, and leisure-time physical activity every 2 years during the follow-up. The correlation coefficient between self-reported weight and measured weight was 0.96. Physical activity was estimated by using the cumulative average number of hours per week on the basis of the reported time spent doing specific activities. Each activity was weighted by its intensity level. The validity of self-reported physical activity in this cohort was reported previously (31).

Identification of Cases of Cholecystectomy

We inquired about occurrence and date of cholecystectomy on each biennial questionnaire starting in 1980. A validation study of the self-report was conducted in a random sample of 50 nurses who reported a cholecystectomy. Forty-three out of 50 participants responded, and of these, all reiterated their earlier report, and the diagnosis of gallstone disease was confirmed in all 36 for whom medical records could be obtained (32). Moreover, more than 80% of the women in our cohort who had a cholecystectomy between 1980 and 1986

reported a diagnosis of symptomatic gallstone disease during that time period. We chose cholecystectomy as the primary end point mainly because symptomatic gallstones are the principal indication for cholecystectomy (33). In contrast, only a minor proportion of asymptomatic gallstones are diagnosed, typically incidentally, making this clinically less relevant condition and unreliable end point.

Statistical Analysis

We first examined the distribution of risk factors for gallstone disease and population characteristics across categories of use of statins or general cholesterol-lowering drugs, which were standardized using the cohort age distribution. We calculated person-time for each participant from the date of return of the 1994 questionnaire to the date of cholecystectomy, cancer, date of last questionnaire return, death, or the end of the study period, whichever came first. In this prospective cohort, women who had undergone cholecystectomy were censored and excluded from subsequent follow-up. Thus, the eligible population at risk comprised only those who remained free of cholecystectomy at the beginning of each two-year follow-up interval. In the analyses women were categorized according to status of use of statins or general cholesterol-lowering drugs. In the main analysis, we used current use of statins as the primary exposure of interest and examined its associations with occurrence of cholecystectomy, where the reference group was statin nonuse. Incidence rates were calculated by dividing the number of events by person-years of follow-up in each category. Relative risks were calculated as the incidence rate of cholecystectomy among women in different categories of exposure compared with the incidence rate among women in the reference category. Age-adjusted relative risks were calculated using the Mantel-Haenszel summary estimator (34). Multivariate relative risks were computed using the Cox proportional hazards regression model (35). We used the most updated information for all covariates prior to each two-year interval. The covariates that were selected were those that were previously observed to be associated with gallstone disease in this cohort or that have been consistently found to be associated with risk in the literature. Thus, we adjusted for the following known or suspected risk factors in multivariate analyses: age, time period (2-year intervals), body mass index at the beginning of each two-year follow-up interval (<20.00, 20.00-22.49, 22.50-24.99, 25.00-27.49, 27.50-29.99, 30.00-32.49, 32.50-34.99, 35.00-37.49, 37.50-39.99, and ≥40), weight change in the previous two years (≥10 pound weight loss, 5.0-9.9 pound weight loss, maintained weight ± 4.9 pounds, 5.0-9.9 pound weight gain, ≥10 pound weight gain), parity (0, 1, 2-3, ≥4 births), oral contraceptive use (ever, never), hormone replacement therapy (premenopausal, postmenopausal without hormone replacement therapy, postmenopausal with past hormone replacement therapy, and postmenopausal with current hormone replacement therapy), physical activity (quintiles), pack-years of smoking (0, 1-9, 10-24, 25-44, 45-64, ≥65), thiazide diuretics (yes or no), non-steroidal anti-inflammatory drugs (0, 1-6, ≥7 times per week, and dose unknown), intake of total energy (quintiles), energy-adjusted dietary fiber (quintiles), energy-adjusted protein (quintiles), energy-adjusted carbohydrate (quintiles), alcohol (0, 0.1-4.9, 5.0-14.9, 15.0-29.9, ≥30.0 grams per day), coffee (0, 1, 2-3, 4+ cups per day), saturated fat, *trans* fat, and polyunsaturated fat (quintiles). Goodness-of-fit statistics were used to assess the model fit (34). We conducted various analyses to address the possibilities that preclinical symptoms or health-seeking behavior related to gallstone disease might bias our results by creating spurious associations. In addition, for potential effect modification we conducted stratified analyses to determine whether risk associated with use of statins was modified by other risk factors for gallstone disease. Tests for interaction were performed using likelihood ratio tests by comparing two nested models, one with the main effects only and the other with both the main effects and interaction terms. All relative risks are presented with 95% confidence intervals (C.I.), and

all reported p-values are two-sided. All analyses were performed with Statistical Analysis System software, release 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

According to statin use in 2000 (table 1), compared with statin nonusers, current statin users tended to have a higher prevalence of diabetes, tended to be heavier, exercise less, smoke more, consume more protein, carbohydrate, and dietary fiber, but less alcohol, coffee, and saturated fatty acids. Current statin users also tended to have a higher prevalence of use of thiazide diuretics, oral contraceptives, and hormone replacement, but lower prevalence of aspirin use.

In the statin analysis we ascertained 2,479 cases of cholecystectomy during 305,197 person-years of follow-up between 1994 and 2000. In the age-adjusted analysis, as compared with statin nonuse, the estimated relative risk of cholecystectomy of current statin use was 0.96 (95% confidence interval (C.I.), 0.82 to 1.12) (model 1, table 2). This association between current statin use and risk of cholecystecomy was strengthened after further adjustment for other known risk factors for gallstone disease. In an analysis that included age, body mass index, recent weight change, parity, oral contraceptive use, hormone replacement therapy, physical activity, pack-years of smoking, thiazide diuretics, non-steroidal anti-inflammatory drugs, total energy intake, dietary fiber, protein, alcohol, coffee, carbohydrate, and saturated, *trans*, and polyunsaturated fats (model 2, table 2), the relative risk for current statin use, compared with statin nonuse, was 0.82 (95% C.I., 0.70 to 0.96).

To further examine if duration of current statin use was associated with risk, we created three categories of duration of use (<2 years, 2-4 years, >4 years). Because there were few cases in the category of more than 4 years, categories of duration of current statin use were collapsed into two (<2 years, ≥2 years) for the analysis (table 2). Compared with statin nonuse, the relative risk for current statin use of less than 2 years was 0.83 (95% C.I., 0.68 to 1.01), and the relative risk for current statin use of 2 or more years was 0.81 (95% C.I., 0.62 to 1.06) (model 2, table 2).

We additionally incorporated the prospective follow-up period from 2000 to 2004 in the analysis, and examined the relation of statin use to the occurrence of cholecystectomy between 1994 and 2004. Compared with statin nonuse, the multivariate relative risk for current statin use was 0.88 (95% C.I., 0.78 to 0.99). The multivariate relative risk for current statin use of less than 2 years was 0.92 (95% C.I., 0.80 to 1.07), and the relative risk for current statin use of 2 or more years was 0.81 (95% C.I., 0.68 to 0.97).

In the general cholesterol-lowering drugs analysis, during 511,411 person-years of follow-up, we ascertained 3,420 cases of cholecystectomy between 1994 and 2004. In the age-adjusted analysis, as compared with general cholesterol-lowering drugs nonuse, the relative risk of cholecystectomy for current general cholesterol-lowering drugs use was 1.04 (95% C.I., 0.93 to 1.16) (model 1, table 3). This association between current general cholesterol-lowering drugs use and risk of cholecystecomy was strengthened (relative risk 0.88, 95% C.I., 0.79 to 0.98) after further adjustment for other known risk factors for gallstone disease (model 2, table 3). To further examine if duration of general cholesterol-lowering drugs use was associated with risk, we created three categories of duration of use (<2 years, 2-4 years, >4 years). Duration of general cholesterol-lowering drugs use was not significantly associated with risk of cholecystectomy (model 2, table 3).

To examine whether the association between current statin use and risk of cholecystecomy was modified by other risk factors for gallstones, we repeated the multivariate analyses within subgroups of risk factors (table 4). We found no apparent effect modification (non-

significant tests of interaction in the stratified subgroups, all p values > 0.1). The inverse associations between current statin use and risk of cholecystectomy persisted, although they were not always statistically significant, which would in part be due to reduced sample sizes in the subgroups. Among diabetic women, duration of current statin use (<2 years, ≥2 years) was correlated with risk of cholecystectomy; compared with statin nonuse, the relative risk for current statin use of less than 2 years was 0.67 (95% C.I., 0.37 to 1.21), and the relative risk for current statin use of 2 or more years was 0.25 (95% C.I., 0.07 to 0.88). Duration of current statin use was not significantly associated with risk of cholecystectomy among non-diabetic women.

To rule out preclinical disease affecting the association between current statin use and risk of cholecystectomy, we repeated the analysis excluding cases in the first two years of follow-up. The multivariate relative risk for current statin use, compared with statin nonuse, remained significant (relative risk 0.81, 95% C.I., 0.68 to 0.97).

It is possible that health care-seeking behavior might create a spurious association between current statin use and risk of cholecystectomy. To evaluate the potential of detection bias due to increased medical surveillance, we additionally excluded women without a routine medical check-up between 1992 and 1994. The multivariate relative risk for current statin use, compared with statin nonuse, remained significant (relative risk 0.78, 95% C.I., 0.66 to 0.93).

DISCUSSION

In this large cohort study among women, we found that statin use was associated with a reduced risk of cholecystectomy. We evaluated whether confounding could explain the observed inverse associations. Adjustments for these potential confounding variables including other lifestyle or dietary factors did not attenuate, but, rather, strengthened the associations. A decreased risk persisted in the multivariate analyses, which indicated that the associations were independent of these known risk factors. Residual confounding by unknown risk factors is theoretically possible, but the stronger associations with additional adjustment of a multitude of known or suspected risk factors in the multivariate models argued against this (36). Although residual confounding by indication is possible, it is unlikely to bias the association as serum cholesterol levels are unrelated to risk for gallstones (5). We cannot conclusively exclude the possibility that some unknown factor, such as socioeconomic status, associated with statin use might be responsible for the risk reduction as in any observational study. However the population we studied is relatively homogeneous with respect to education and occupation, confounding by socioeconomic status was minimized.

This study has several strengths, including a large number of participants and cases, detailed exposure and covariate information, and high levels of follow-up. Because all participants are registered nurses familiar with health-related exposures and prescription medications, our exposure data are likely to be accurate. Except for the statin inquiry in 2000, exposure data were collected before the end point of cholecystectomy, precluding the possibility of recall bias.

Clinical and experimental studies on statins have raised hopes that statins may provide benefits beyond reducing serum cholesterol levels and risk of cardiovascular disease. The principal potential clinical application of statins in hepatobiliary disorders is for the treatment or prevention of gallstone disease. Available studies of the effects of statins on gallstone disease, however, have not been conclusive. Statins have been found to suppress biliary cholesterol secretion and saturation, unrelated to modulation of cholesterol synthesis.

In an experiment of pravastatin use in humans, it was found that pravastatin reduced the secretion of all biliary lipids during an experimental period in which cholesterol synthesis was unchanged, and, after long-term pravastatin administration, cholesterogenesis was found to have no direct influence on biliary cholesterol secretion (13). Another possible mechanism of action of statins on gallstone disease is inhibition of cholesterol crystal nucleation (21), although results have not been consistent (37-39). Several studies reported a promising effect of statins on gallstone dissolution (7, 24, 40, 41); however, the beneficial effect of gallstone dissolution was not shown in other studies (42). The inconsistency among these studies may be, in part, due to potential time-dependent or dose-dependent effects as a function of the type of statin (8), small sample size, limited control for potential confounders, or lack of long-term follow-up.

Present knowledge of pleiotropic effects of statins is mainly related to the anti-inflammatory and endothelial effects of this drug class (43-45). The effect of statins on glucose metabolism and insulin sensitivity has been under investigation (46-49). A recent randomized, placebo-controlled trial testing the effect of statins on insulin sensitivity revealed that atorvastatin and simvastatin improved the homeostasis model assessment index, an indirect measurement of insulin resistance, in elderly patients with type 2 diabetes mellitus (46). Statins, however, appear to have no effect on insulin sensitivity in non-diabetics (50). Because the occurrence of gallstone disease has been related to hyperinsulinemia and insulin resistance (51-53), the beneficial effect of statins on insulin sensitivity among diabetics may be the underlying mechanism for the large apparent risk reduction we observed among diabetic women using statins for two or more years in the subgroup analysis.

Despite the fact that all participants in this study are registered nurses who are familiar with prescription drugs, measurement error in our assessment of statin use might be a potential concern because we lacked information regarding the validity of self-reported statin use. However, reporting of other lifestyle factors has been shown to have a high degree of validity and is reproducible in this cohort (54, 55). Moreover, measurement error would tend to dampen results leading toward null findings (34), but should not cause a significant inverse association. Therefore, our results are likely conservative. Our study was limited by the absence of information in regard to dosage of statins, which prevented us from addressing the effect of increasing doses of statins on the risk of cholecystectomy. A further limitation was that our study was designed to evaluate statin use in only two-year intervals, which limited our ability to precisely examine the association between shorter periods of exposure to statin use and risk of cholecystectomy.

It is possible that the restriction of the retrospective analysis to current statin users in 2000 might cause recall bias. To evaluate this possibility, we conducted an alternative prospective analysis of general lipid-lowering drugs in relation to risk of cholecystectomy. In this prospective analysis, women who were current users of general cholesterol-lowering drugs, mostly statins in this cohort, as compared with nonusers, also had a decreased risk of cholecystectomy. Given the high prevalence (93%) of statin use among lipid-lowering drug users in 2000, this is likely a very good approximation of statin use. Any misclassification of other cholesterol-lowering drugs as statins or misclassification of use due to inaccurate self-reporting of the use of these drugs should be non-differential with respect to the end point of cholecystectomy because this analysis was prospective. In any event, the effect of this type of error would lead to a relative risk estimate closer to the no-association value of 1.0. Therefore, the relative risk estimate in this prospective analysis with regard to statin use tends to be conservative. In addition, in this cohort consistently high follow-up rates reduce the possibility that our results are biased by women lost to follow up. Thus, these potential biases should have been minimal. Our findings are unlikely due to biased ascertainment of

cholecystectomy cases, given the study sample of women and the validity of reports of cholecystectomies. Moreover, in prospective follow-up studies any uniform under-ascertainment of cases would not bias the observed relative risks (34).

In conclusion, our findings suggest that use of statins may reduce risk of cholecystectomy in women. Further study, particularly among diabetics, is warranted to evaluate the associations of longer durations of statin use and specific types of statins with risk. Our results should have implications for additional clinical, epidemiological, and mechanistic research.

Acknowledgments

We are indebted to the participants in the Nurses' Health Study for their continuing dedication and commitment to the study. We also thank the research staff in the Nurses' Health Study for their expert assistance.

Grant support for the study: research grants (CA55075 and DK46200) from the National Institute of Health.

REFERENCES

1. Beckingham IJ. ABC of diseases of liver, pancreas, and biliary system. Gallstone disease. BMJ. 2001; 322(7278):91–94. [PubMed: 11154626]
2. National Center for Health Statistics. Advance Data from Vital and Health Statistics. Hyattsville, MD: 2000. National Hospital Discharge Survey.
3. Kang JY, Ellis C, Majeed A, et al. Gallstones – an increasing problem: a study of hospital admissions in England between 1989/1990 and 1999/2000. Aliment Pharmacol Ther. 2003; 17(4): 561–569. [PubMed: 12622765]
4. Dowling RH. Pathogenesis of gallstones. Aliment Pharmacol Ther. 2000; 14(Suppl.2):39–47.
5. Donovan, JM.; Konikoff, FM. Gallstone disease: pathogenesis and treatment. In: Schiff, ER.; Sorrell, MF.; Maddrey, WC., editors. Schiff's Diseases of the Liver. ed 10. Lippincott Williams & Wilkins; Philadelphia: 2007. p. 639-663.
6. Tazuma S, Yamashita G, Ochi H, et al. Effects of cerivastatin sodium, a new HMG-CoA reductase inhibitor, on biliary lipid metabolism in patients with hypercholesterolemia. Clin Ther. 1998; 20(3): 477–485.
7. Tazuma S, Kajiyama G, Mizuno T, et al. A combination therapy with simvastatin and ursodeoxycholic acid is more effective for cholesterol gallstone dissolution than is ursodeoxycholic acid monotherapy. J Clin Gastroenterol. 1998; 26(4):287–291.
8. Tazuma S, Takizawa I, Kunita T, et al. Effects of long-term treatment with low-dose pravastatin on biliary lipid and bile acid composition in patients with nonfamilial hyperlipoproteinemia. Metabolism. 1995; 44(11):1410–1412.
9. Hawk E, Viner JL. Statins and cancer--beyond the "one drug, one disease" model. N Engl J Med. 2005; 352(21):2238–2239.
10. Poynter JN, Gruber SB, Higgins PD, et al. Statins and the risk of colorectal cancer. N Engl J Med. 2005; 352(21):2184–2192.
11. Hoffmann P, Roumeguere T, Schulman C, et al. Use of statins and outcome of BCG treatment for bladder cancer. N Engl J Med. 2006; 355(25):2705–2707.
12. Lubitz SA, Pinney S, Wisnivesky JP, et al. Statin therapy associated with a reduced risk of chronic renal failure after cardiac transplantation. J Heart Lung Transplant. 2007; 26(3):264–272.
13. Kallien G, Lange K, Stange EF, et al. The pravastatin-induced decrease of biliary cholesterol secretion is not directly related to an inhibition of cholesterol synthesis in humans. Hepatology. 1999; 30(1):14–20.
14. Nicholls SJ, Tuzcu EM, Sipahi I, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA. 2007; 297(5):499–508.
15. Rogers SL, Magliano DJ, Levison DB, et al. A dose-specific meta-analysis of lipid changes in randomized controlled trials of atorvastatin and simvastatin. Clin Ther. 2007; 29(2):242–252.

16. Mitchell JC, Logan GM, Stone BG, et al. Effects of lovastatin on biliary lipid secretion and bile acid metabolism in humans. J Lipid Res. 1991; 32(1):71–78.
17. Duane WC, Hunninghake DB, Freeman ML, et al. Simvastatin, a competitive inhibitor of HMG-CoA reductase, lowers cholesterol saturation index of gallbladder bile. Hepatology. 1988; 8(5): 1147–1150.
18. Hoogerbrugge-vd Linden N, de Rooy FW, Jansen H, et al. Effect of pravastatin on biliary lipid composition and bile acid synthesis in familial hypercholesterolaemia. Gut. 1990; 31(3):348–350.
19. Porsch-Ozcurumez M, Hardt PD, Schnell-Kretschmer H, et al. Effects of fluvastatin on biliary lipids in subjects with an elevated cholesterol saturation index. Eur J Clin Pharmacol. 2001; 56(12):873–879.
20. Saunders KD, Cates JA, Abedin MZ, et al. Lovastatin inhibits gallstone formation in the cholesterol-fed prairie dog. Ann Surg. 1991; 214(2):149–154.
21. Tazuma S, Hatsushika S, Aihara N, et al. Inhibitory effects of pravastatin, a competitive inhibitor of hydroxymethylglutaryl coenzyme A reductase, on cholesterol gallstone formation in prairie dogs. Digestion. 1992; 51(3):179–184.
22. Abedin MZ, Narins SC, Park EH, et al. Lovastatin alters biliary lipid composition and dissolves gallstones: a long-term study in prairie dogs. Dig Dis Sci. 2002; 47(10):2192–2210.
23. Smit JW, van Erpecum KJ, Renooij W, et al. The effects of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor pravastatin on bile composition and nucleation of cholesterol crystals in cholesterol gallstone disease. Hepatology. 1995; 21(6):1523–1529.
24. Smit JW, van Erpecum KJ, Stolk MF, et al. Successful dissolution of cholesterol gallstone during treatment with pravastatin. Gastroenterology. 1992; 103(3):1068–1070.
25. Smith JL, Roach PD, Wittenberg LN, et al. Effects of simvastatin on hepatic cholesterol metabolism, bile lithogenicity and bile acid hydrophobicity in patients with gallstones. J Gastroenterol Hepatol. 2000; 15(8):871–879.
26. Colditz GA, Manson DM, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Women's Health. 1997; 6:49–62.
27. Lemaitre RN, Furberg CD, Newman AB, et al. Time trends in the use of cholesterol-lowering agents in older adults: the Cardiovascular Health Study. Arch Intern Med. 1998; 158(16):1761–1768.
28. Siegel D, Lopez J, Meier J. Use of cholesterol-lowering medications in the United States from 1991 to 1997. Am J Med. 2000; 108(6):496–499.
29. Willett, WC. Nutritional epidemiology. 2nd ed. Oxford University Press; New York: 1998.
30. US Department of Agriculture. Composition of foods-raw, processed, and prepared, 1963-1992. Department of Agriculture, US Government Printing Office; Washington, DC: 1993. Agricultural handbook no. 8 series
31. Leitzmann MF, Rimm EB, Willett WC, et al. Recreational physical activity and the risk of cholecystectomy in women. N Engl J Med. 1999; 341(11):777–784.
32. Maclure KM, Hayes KC, Colditz GA, et al. Weight, diet, and the risk of symptomatic gallstones in middle-aged women. N Engl J Med. 1989; 321:563–569.
33. Sleisenger, MH.; Fordtran, JS., editors. Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. WB Saunders; Philadelphia: 2002.
34. Rothman, KJ.; Greenland, S.; Lash, TL. Modern epidemiology. Lippincott Williams & Wilkins; Philadelphia: 2008.
35. Cox, DR.; Oakes, D. Analysis of survival data. Chapman & Hall; London: 1984.
36. Flanders WD, Khoury MJ. Indirect assessment of confounding: graphic description and limits on effect of adjusting for covariates. Epidemiology. 1990; 1:239–246.
37. Smit JW, Van Erpecum KJ, Portincasa P, et al. Effects of simvastatin and cholestyramine on bile lipid composition and gall bladder motility in patients with hypercholesterolaemia. Gut. 1995; 37(5):654–659.
38. Sharma BC, Agarwal DK, Baijal SS, et al. Pravastatin has no effect on bile lipid composition, nucleation time, and gallbladder motility in persons with normal levels of cholesterol. J Clin Gastroenterol. 1997; 25(2):433–436.

39. Smit JW, Van Erpecum KJ, Gadella MM, et al. Does the HMG-CoA reductase inhibitor pravastatin influence nucleation of cholesterol crystals in supersaturated model bile? Eur J Gastroenterol Hepatol. 1996; 8(3):197–200.
40. Saunders KD, Cates JA, Abedin MZ, et al. Lovastatin and gallstone dissolution: a preliminary study. Surgery. 1993; 113(1):28–35.
41. Chapman BA, Burt MJ, Chisholm RJ, et al. Dissolution of gallstones with simvastatin, an HMG CoA reductase inhibitor. Dig Dis Sci. 1998; 43(2):349–353.
42. Smit JW, VanErpecum KJ, VanBerge-Henegouwen GP. Cholesterol synthesis inhibitors in cholesterol gallstone disease. Scand J Gastroenterol Suppl. 1996; 218:56–60.
43. Sommeijer DW, MacGillavry MR, Meijers JC, et al. Anti-inflammatory and anticoagulant effects of pravastatin in patients with type 2 diabetes. Diabetes Care. 2004; 27(2):468–473.
44. Rosenson RS, Tangney CC, Casey LC. Inhibition of proinflammatory cytokine production by pravastatin. Lancet. 1999; 353(9157):983–984.
45. Rosenson RS, Tangney CC. Anti-atherothrombotic properties of statins: implications for cardiovascular event reduction. JAMA. 1998; 279(20):1643–1650.
46. Paolisso G, Barbagallo M, Petrella G, et al. Effects of simvastatin and atorvastatin administration on insulin resistance and respiratory quotient in aged dyslipidemic non-insulin dependent diabetic patients. Atherosclerosis. 2000; 150(1):121–127.
47. Paolisso G, Sgambato S, De Riu S, et al. Simvastatin reduces plasma lipid levels and improves insulin action in elderly, non-insulin dependent diabetics. Eur J Clin Pharmacol. 1991; 40(1):27–31.
48. Pontrelli L, Parris W, Adeli K, et al. Atorvastatin treatment beneficially alters the lipoprotein profile and increases low-density lipoprotein particle diameter in patients with combined dyslipidemia and impaired fasting glucose/type 2 diabetes. Metabolism. 2002; 51(3):334–342.
49. Nielsen S, Schmitz O, Moller N, et al. Renal function and insulin sensitivity during simvastatin treatment in type 2 (non-insulin-dependent) diabetic patients with microalbuminuria. Diabetologia. 1993; 36(10):1079–1086.
50. Gannage-Yared MH, Azar RR, Amm-Azar M, et al. Pravastatin does not affect insulin sensitivity and adipocytokines levels in healthy nondiabetic patients. Metabolism. 2005; 54(7):947–951.
51. Misciagna G, Guerra V, Di Leo A, et al. Insulin and gall stones: a population case control study in southern Italy. Gut. 2000; 47(1):144–147.
52. Tsai CJ, Leitzmann MF, Willett WC, et al. Glycemic load, glycemic index, and carbohydrate intake in relation to risk of cholecystectomy in women. Gastroenterology. 2005; 129(1):105–112.
53. Tsai CJ, Leitzmann MF, Willett WC, et al. Macronutrients and insulin resistance in cholesterol gallstone disease. Am J Gastroenterol. 2008; 103(11):2932–2939.
54. Rimm EB, Stampfer MJ, Colditz GA, et al. Validity of self-reported waist and hip circumferences in men and women. Epidemiology. 1990; 1(6):466–473.
55. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc. 1993; 93(7):790–796.

Table 1

Age and age-standardized characteristics of 53,611 U.S. women according to statin use in 2000 in the Nurses' Health Study

Characteristics		Current statin users		
	Nonusers (n=45,615)	< 2 years (n=3,530)	2-4 years (n=2,708)	> 4 years (n=1,758)
Current age (years) *	65.9	66.2	66.0	64.8
Current body mass index (kg/m^2) *	25.7	26.9	26.9	26.7
Physical activity (METs) *[a]	13.7	12.7	12.8	13.2
Any weight loss in prior 2 yrs (%)	37.5	36.7	36.4	37.0
History of oral contraceptive use (%)	51.9	51.4	52.2	57.4
Current use of HRT (%)[b]	52.8	52.6	55.7	59.6
History of diabetes (%)	5.0	11.5	10.5	10.1
Regular use of aspirin (%)	45.3	33.2	33.3	32.6
Regular use of thiazide diuretics (%)	8.3	12.5	12.9	11.4
Pack-years of smoking *	15.5	17.6	17.7	18.6
Protein (g/d) *	74.2	75.6	75.4	76.1
Carbohydrate (g/d) *	209	213	215	216
Alcohol (g/d) *	5.4	4.6	4.7	4.3
Coffee (cups) *	1.3	1.1	1.2	1.2
Saturated fat (g/d) *	17.4	16.3	15.9	15.6
Polyunsaturated fat (g/d) *	9.2	9.1	9.1	9.1
Trans fat (g/d) *	2.4	2.3	2.3	2.3
Dietary fiber (g/d) *	18.8	19.2	19.4	19.4

*Values expressed as means

[a]Metabolic equivalent tasks per week, defined as a multiple of metabolic equivalent of sitting at rest.

[b]HRT = hormone replacement therapy. Only postmenopausal women were included.

Table 2

Adjusted relative risks of cholecystectomy according to statin use among US women in the Nurses' Health Study: retrospective analysis [a]

Variable	Nonuse	Current use		
		< 2 years	≥ 2 years[c]	Total
Cases	2,412	113	54	167
Person-years	283,633	13,907	7,657	21,564
Model 1: Age-adjusted (95% C.I.)[b]	1.00 (referent)	0.97 (0.80, 1.18)	0.93 (0.71, 1.22)	0.96 (0.82, 1.12)
Model 2: Multivariate (95% C.I.)[b]	1.00 (referent)	0.83 (0.68, 1.01)	0.81 (0.62, 1.06)	0.82 (0.70, 0.96)

Model 2: Relative risk adjusting for age, time period, body mass index at the beginning of each two-year follow-up interval, weight change in the previous two years, parity, oral contraceptive use, hormone replacement therapy, physical activity, pack-years of smoking, thiazide diuretics, non-steroidal anti-inflammatory drugs, intake of total energy, energy-adjusted dietary fiber, energy-adjusted protein, energy-adjusted carbohydrate, alcohol, coffee, saturated fat, *trans* fat, and polyunsaturated fat.

[a] Retrospective assessment between 1994 and 2000

[b] C.I. = confidence interval.

[c] The categories of 2-4 years and >4 years were collapsed into one category due to few cases in the category of >4 years.

Table 3

Adjusted relative risks of cholecystectomy according to general lipid-lowering drugs use among US women in the Nurses' Health Study: prospective analysis [a]

	Nonuse	Past use	Current use			
Variable			**< 2 years**	**2-4 years**	**> 4 years**	**Total**
Cases	2,979	62	184	109	86	379
Person-years	443,049	8,826	27,975	14,885	16,676	59,536
Model 1: Age-adjusted (95% C.I.)[b]	1.00 (referent)	1.12 (0.87, 1.45)	1.07 (0.92, 1.25)	1.01 (0.83, 1.22)	1.02 (0.82, 1.27)	1.04 (0.93, 1.16)
Model 2: Multivariate (95% C.I.)[b]	1.00 (referent)	0.99 (0.77, 1.28)	0.91 (0.79, 1.06)	0.84 (0.69, 1.03)	0.86 (0.69, 1.07)	0.88 (0.79, 0.98)

Model 2: The multivariate model included the same covariates as in model 2 in table 2.

[a] Prospective assessment with follow-up between 1994 and 2004.

[b] C.I. = confidence interval.

Table 4

Multivariate relative risks of cholecystectomy in relation to statin use according to selected risk factors among US women in the Nurses' Health Study[a]

Variables	Nonuse (referent)	Current use Multivariate relative risk (95% C.I.)[b]		
		< 2 years	≥ 2 years	Total
Diabetes				
Yes	1.00	0.67 (0.37, 1.21)	0.25 (0.07, 0.88)	0.53 (0.31, 0.93)
No	1.00	0.82 (0.67, 1.01)	0.85 (0.64, 1.13)	0.83 (0.70, 0.99)
Diuretic use				
Yes	1.00	0.68 (0.40, 1.16)	0.72 (0.34, 1.52)	0.69 (0.44, 1.08)
No	1.00	0.84 (0.69, 1.04)	0.83 (0.62, 1.12)	0.84 (0.70, 0.99)
Body mass index (kg/m^2)				
< 30	1.00	0.90 (0.72, 1.14)	0.88 (0.64, 1.21)	0.89 (0.74, 1.08)
≥ 30	1.00	0.79 (0.55, 1.13)	0.87 (0.50, 1.50)	0.81 (0.60, 1.09)
Weight change within past 2 yrs				
> 4 lb	1.00	1.03 (0.74, 1.44)	0.47 (0.21, 1.02)	0.88 (0.64, 1.20)
≤ 4 lb	1.00	0.82 (0.64, 1.05)	0.99 (0.73, 1.34)	0.88 (0.72, 1.07)
Current smoking				
Yes	1.00	0.79 (0.42, 1.50)	0.83 (0.32, 2.12)	0.80 (0.47, 1.38)
No	1.00	0.83 (0.68, 1.01)	0.82 (0.62, 1.09)	0.82 (0.69, 0.97)
Current age				
< 60	1.00	0.59 (0.40, 0.88)	0.79 (0.46, 1.37)	0.65 (0.47, 0.90)
≥ 60	1.00	0.93 (0.75, 1.16)	0.81 (0.60, 1.12)	0.89 (0.75, 1.08)
Physical activity[c] (METs)				
High	1.00	0.88 (0.70, 1.11)	0.85 (0.62, 1.18)	0.87 (0.72, 1.05)
Low	1.00	0.74 (0.52, 1.05)	0.70 (0.42, 1.18)	0.73 (0.54, 0.98)
Coffee intake[c]				
High	1.00	0.89 (0.70, 1.13)	0.77 (0.52, 1.12)	0.85 (0.69, 1.04)

Variables	Nonuse (referent)	Current use Multivariate relative risk (95% C.I.)[b]		
		< 2 years	≥ 2 years	Total
Low	1.00	0.74 (0.54, 1.02)	0.89 (0.60, 1.34)	0.79 (0.61, 1.02)

[a] The multivariate model included the same covariates as in model 2 in table 2. In each case, the stratification variable was excluded from the model. Within each stratum, the group without use of statins served as the reference group.

[b] C.I. = confidence interval

[c] Median values were used as cut-off point.