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Personal history of gallstones and risk of incident psoriasis and psoriatic arthritis in U.S. women

Lana X Tong^{1,2,*}, Shaowei Wu^{1,3,*}, Tricia Li^{1,3}, Abrar A Qureshi^{1,3,4}, Edward L Giovannucci^{4,5}, and Eunyoung Cho^{3,4}

¹Department of Dermatology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

²Department of Health Policy and Management, Harvard School of Public Health, Boston, MA

³Department of Dermatology, Warren Alpert Medical School, Brown University, Providence, RI

⁴Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

⁵Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA

Abstract

Background—Metabolic syndrome has been associated with both gallstones and psoriasis, suggesting a potential biological linkage between gallstones and psoriasis. However, the association between gallstones and psoriasis has not yet been studied.

Objective—To investigate the association between gallstones and psoriasis.

Design—Prospective cohort study.

Setting—Nurses' Health Study II (1991-2005).

Participants—89,230 women aged 25 to 42 years who were free of psoriasis at baseline and responded to a 2005 follow-up questionnaire regarding their diagnosis of psoriasis.

Main Outcomes and Measures—Relative risk (RR) of developing psoriasis or psoriatic arthritis (PsA), which were self-reported and validated by supplemental questionnaires.

Results—In this population of women, 2,206 participants had gallstones confirmed by a history of cholecystectomy at baseline. A total of 642 individuals had a diagnosis of incident psoriasis, of which 157 had concomitant PsA. After adjusting for known risk factors of psoriasis besides body mass index (BMI), a baseline history of cholecystectomy-confirmed gallstones was associated with increased risk of psoriasis (multivariate-adjusted RR = 2.20, 95% CI: 1.56, 3.10) and concomitant PsA (multivariate-adjusted RR = 4.41, 95% CI: 2.70, 7.18). After additionally

Corresponding author: Eunyoung Cho, ScD, Department of Dermatology, Warren Alpert, Medical School of Brown University, 339 Eddy St, Providence, RI 02903, eunyoung_cho@brown.edu, Tel: 617-525-2089, Fax: 617-525-2008.

*These authors contributed equally to this work.

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adjusting for BMI, the fully-adjusted RRs associated with a history of cholecystectomy-confirmed gallstones were 1.70 (95% CI: 1.20,2.41) for psoriasis and 2.96 (95% CI: 1.80, 4.89) for PsA.

Conclusions and Relevance—Personal history of gallstones was associated with an increased risk of psoriasis and PsA, independent of obesity in a cohort of US women.

Keywords

cholecystectomy; psoriasis; psoriatic arthritis; gallstones; women

Introduction

Gallstone disease (GSD) is a major health condition, and is thought to affect 10-15% of adults in the United States and incur an estimated health care cost of approximately \$6.2 billion annually.¹⁻³ GSD is a leading cause of gastrointestinal-related hospital admissions as well.⁴ Previous studies have demonstrated that metabolic syndrome, a prevalent cardiovascular condition, is a strong risk factor for GSD, and the link between metabolic syndrome and GSD may be due to cholesterol, which becomes dysregulated in metabolic syndrome and also makes up over 80% of gallstones.⁵ Inflammation secondary to a macrophage-mediated stress response may also be a potential contributor to the development of GSD.⁶

Psoriasis is a chronic inflammatory T-cell mediated skin disease with joint involvement in about 30% of patients.⁷ An estimated 2-3% of the general population suffers from psoriasis, and over 520,000 individuals in the United States are estimated to be affected by psoriatic arthritis (PsA).⁸⁻¹¹ Activation of systemic inflammatory pathways and the resulting chronic inflammation is thought to predispose psoriasis patients to a number of conditions, such as obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM) and cardiovascular disease.¹²⁻¹⁵ Moderate to severe psoriasis has been particularly associated with metabolic syndrome and obesity, and it has even been postulated that the relationship between psoriasis and obesity is bidirectional based on the fact that both diseases involve chronic inflammatory processes.¹⁶⁻¹⁸

Metabolic syndrome and obesity are known to be strongly associated with both psoriasis and gallstones, implying a potential biological linkage between these two diseases.^{5,19} However, the relationship between GSD and psoriasis/PsA has not yet been studied. To address the hypothesis that GSD and psoriasis/PsA may be associated with each other, we investigated the association of interest based on a large cohort of U.S. women, the Nurses' Health Study II (NHSII).

Materials and Methods

Study Population

In 1989, 116,430 female registered nurses between the ages of 25 and 42 years enrolled in the NHSII by completing an initial questionnaire that inquired about lifestyle factors and medical history. This cohort was followed using biennially mailed questionnaires that asked about life-style factors and newly diagnosed diseases, with a response rate of over 90% for

each follow-up cycle. The institutional review board of the Partners Health Care System approved the study protocol. Completion and return of the self-administered questionnaire were considered informed consent.

Ascertainment of Gallstone Disease

In biennial questionnaires, participants were asked if they had ever undergone a cholecystectomy or had received a diagnosis of gallstones from a physician, as well as if their gallstones were symptomatic or if the diagnosis had been confirmed radiographically. Self-reported GSD, including symptomatic unremoved gallstones and cholecystectomy, was previously confirmed in a random sample of 441 participants in a similar prospective study of male health professionals, whose medical records were verified in 99%.²⁰

Ascertainment of Psoriasis and PsA Cases

In 2005, participants were asked if they had ever received a diagnosis of psoriasis from a physician as well as the date of diagnosis (before 1991, 1991-1994, 1995-1998, 1999-2002, or 2003-2005). A total of 2,586 participants reported a history of physician-diagnosed psoriasis. Self-reported psoriasis was confirmed using the Psoriasis Screening Tool (PST) questionnaire, which inquires about symptoms and the types of clinicians (dermatologist or other physician specialty) making the diagnosis and has been demonstrated to have 99% sensitivity and 94% specificity for psoriasis screening.²¹ A diagnosis of concomitant PsA was ascertained with the PsA Screening and Evaluation (PASE) questionnaire, which asks patients to rate their symptoms and function on a scale. An overall score of 47 has been shown to have 70-82% sensitivity and 73-80% specificity for PsA identification in pilot studies.²²⁻²⁴ We confirmed a total of 1,600 psoriasis diagnoses using PST. Among these participants, 348 were confirmed to have concomitant PsA using PASE.

Assessment of Covariates

A semiquantitative food-frequency questionnaire (FFQ) was first mailed to NHS II in 1991 that asked about the average use of over 130 foods and beverages during the previous year. The reproducibility and validity of the FFQ has been documented elsewhere,²⁵ and was mailed to participants every 4 years. Nutrient intake was determined from the United States Department of Agriculture information on nutrient content and reported frequency of consumption of each specified food item. Information on supplemental calcium use was collected from use of multivitamins and individual supplements.

Height and ethnicity were assessed in the baseline questionnaire. Information on body weight, smoking status and number of cigarettes smoked per day, and history of chronic diseases (i.e., cardiovascular disease, type 2 diabetes, hypertension, and hypercholesterolemia) was updated through the biennial questionnaires. Body mass index (BMI) was determined by dividing weight in kilograms by the square of height in meters.

Statistical Analysis

Analysis was restricted to participants who responded to a 2005 follow-up questionnaire regarding their diagnosis of psoriasis. We excluded 1,007 participants who did not respond to the PST or PASE questionnaires or did not have a confirmatory response, 895 with

baseline psoriasis before 1991, 34 who were diagnosed with psoriasis/PsA but had missing diagnosis date, and 8 who were diagnosed with psoriasis/PsA but had missing BMI. Chi-square tests for categorical variables and t tests for continuous variables were used to compare the baseline characteristics of participants with and without gallstones. Person-year of follow-up for each participant was calculated from the return date of the baseline questionnaire (1991) to the diagnosis date of psoriasis/PsA or the end of follow-up (June 2005), whichever came first. Date of diagnosis of psoriasis/PsA was assigned as the median of reported diagnosis period. Relative risks (RRs) and 95% confidence intervals (CIs) for the association between a personal history of gallstones and risk of psoriasis/PsA were computed using COX proportional hazards models. Multivariate-adjusted RRs for psoriasis and psoriasis with concomitant PsA were calculated after adjusting for known risk factors for psoriasis/PsA: age, smoking status (never, past, current smoker with 1-14, 15-24, or 25 cigarettes/day), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9 or 27.0 metabolic equivalent hours/week), alcohol intake (none, <5.0, 5.0-9.9, 10.0-19.9, 20.0 g/d) and ethnicity (white, Asian, Hispanic, African American). RRs were then adjusted further by BMI (continuous). Additional adjustment was performed for potential intermediate variables between GSD and psoriasis/PsA, i.e. potential markers for metabolic syndrome: personal histories of cardiovascular disease (CVD), hypertension, T2DM and hypercholesterolemia.

We used two definitions for gallstones: symptomatic or radiographically confirmed gallstones and cholecystectomy-confirmed gallstones. We also examined baseline and updated history of gallstones and the risk of psoriasis/PsA. In sensitivity analyses, we additionally adjusted for potential risk factors for gallstones in the multivariate models, using the updated history of gallstones as the exposure. All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute). All statistical tests were 2-tailed, and the significance level was set at $P < 0.05$.

Results

A total of 89,230 participants were included in the present study, and 642 incident cases of psoriasis were confirmed over 1,233,042 years of follow-up. Of the participants with confirmed psoriasis, 157 also had concomitant PsA. Baseline characteristics of these participants are shown in Table 1. Participants with a history of cholecystectomy ($n = 2,206$) tended to have a higher mean BMI and higher prevalence of T2DM, hypertension, hypercholesterolemia, and were more likely to smoke cigarettes and less likely to be physically active or consume alcohol than those without gallstones. Among those with a known history of gallstones, included and excluded participants with psoriasis were compared. Baseline comorbidities (as listed in Table S1) between these groups were similar.

Table 2 presents the association between a personal history of gallstones and risk of psoriasis. Both an updated history of cholecystectomy-confirmed gallstones (multivariate RR = 1.53, 95% CI: 1.19, 1.96) and an updated history of symptomatic/radiographically-confirmed gallstones (multivariate RR = 1.38, 95% CI: 1.08, 1.75) were associated with an increased risk of developing psoriasis. This positive association appeared to be stronger when a baseline history of GSD was evaluated (multivariate RR = 2.20, 95% CI: 1.56, 3.10 for cholecystectomy-confirmed gallstones; multivariate RR = 1.75, 95% CI: 1.30, 2.35 for

symptomatic/radiographically-confirmed gallstones). After additionally adjusting for BMI, a baseline history of GSD continued to be associated with an increased risk of psoriasis (fully-adjusted RR = 1.70, 95% CI: 1.20, 2.41 for cholecystectomy-confirmed gallstones; fully-adjusted RR = 1.36, 95% CI: 1.01, 1.84 for symptomatic/radiographically-confirmed gallstones). When adjusting for potential intermediate variables in the development of GSD and psoriasis/PsA (CVD, hypertension, hypercholesterolemia, T2DM), the association held between a baseline history of cholecystectomy-confirmed gallstones and psoriasis (fully-adjusted RR = 1.65, 95% CI: 1.16, 2.35).

Table 3 presents the association between gallstones and risk of PsA. An updated history of both cholecystectomy-confirmed gallstones (multivariate RR = 3.07, 95% CI: 2.08, 4.55) and an updated history of symptomatic/radiographically-confirmed gallstones (multivariate RR = 2.21, 95% CI: 1.48, 3.29) were associated with an increased risk of developing concomitant PsA as well. Those with a baseline history of cholecystectomy-confirmed gallstones (multivariate RR = 4.41, 95% CI: 2.70, 7.18) or symptomatic/radiographically-confirmed gallstones (RR = 2.55, 95% CI: 1.58, 4.12) also had an increased risk of concomitant PsA. After additionally adjusting for BMI, these associations remained statistically significant except that the association between baseline history of symptomatic/radiographically-confirmed gallstones and PsA became marginally significant. When adjusting for intermediate variables (CVD, hypertension, hypercholesterolemia, T2DM), we found that the association held between a baseline history of cholecystectomy-confirmed gallstones and PsA (fully-adjusted RR = 2.86, 95% CI: 1.72, 4.73).

We then examined the risk of psoriasis/PsA in persons with a history of cholecystectomy and/or symptomatic/radiographically-confirmed gallstones. Because GSD based on the two definitions largely overlap, the associations using the combined definition were similar for risk of psoriasis (age-adjusted RR = 1.51, 95% CI: 1.20, 1.89; multivariate adjusted RR = 1.40, 95% CI: 1.11, 1.76) as well as PsA (age-adjusted RR = 2.89, 95% CI: 1.99, 4.18; multivariate adjusted RR = 2.33, 95% CI: 1.59, 3.41). When adjusting for BMI, the association between GSD and PsA remained significant (fully-adjusted RR = 1.79, 95% CI: 1.21, 2.63) whereas the association between GSD and psoriasis became marginal (fully-adjusted RR = 1.17, 95% CI: 0.93, 1.48). Analyses with additional adjustment for other risk factors for gallstones, including fluid intake, calcium supplements, dietary intakes of calcium, animal protein, potassium, sodium, magnesium, vitamin C, vitamin D, oxalate, and caffeine (all in quintiles), also yielded essentially unchanged RRs (data not shown).

The association between an updated history of cholecystectomy and PsA was modified by BMI. The association between an updated history of cholecystectomy-confirmed gallstones and risk of PsA among women with BMI <30 kg/m² (multivariate RR = 3.18, 95% CI: 1.71, 5.90) was stronger than that among women with BMI ≥ 30 kg/m² (multivariate RR = 1.71, 95% CI: 1.04, 2.85) (*P* for interaction = 0.02).

Discussion

In this study, we examined the association between GSD and incidence of both psoriasis and PsA for the first time in a large cohort of U.S. women. After adjusting for known psoriasis

risk factors and potential confounders, we found that a history of either cholecystectomy-confirmed or symptomatic/radiographically-confirmed gallstones is associated with an increased risk of psoriasis and PsA. The association appeared to be stronger when using baseline history of gallstones as the exposure, suggesting a potential long-term effect of preexisting gallstones. In addition, the association between gallstones and PsA appeared to be modified by BMI, with a stronger positive association observed among women with BMI <30 kg/m² than those with BMI ≥30 kg/m².

Our previous study suggested an apparent association between higher BMI and increasing psoriasis risk in the same study population.¹⁷ However, when we stratified the association between history of GSD and psoriasis, the association was in fact stronger among those with lower BMI. It is possible that when the risk was already elevated due to obesity, having a history of GSD did not have any additional impact.

In several recent case control studies, several risk factors for psoriasis were identified, such as obesity (OR = 1.9, 95% CI: 1.2, 2.8),²⁶ low levels of physical activity (OR = 3.42, 95% CI: 1.47, 7.91), hypertension (OR = 2.5, 95% CI: 1.29, 4.88) and dyslipidemia (OR = 1.91, 95% CI: 1.04, 3.53).²⁷ The risk increase of psoriasis associated with gallstones (fully-adjusted RR = 1.70, 95% CI: 1.20, 2.41 for cholecystectomy-confirmed gallstones at baseline) in our study was similar in magnitude to other well-established risk factors for psoriasis.

Psoriasis is a chronic T-cell mediated inflammatory disease that affects a significant proportion of the general population and can affect the skin, joints, nails and scalp. Patients with PsA generally present with more severe skin manifestations.²⁸ Psoriasis is thought to have a multifactorial etiology involving genetic, environmental and autoimmune factors, and is classified as a Th1-type disease.^{8,29,30} It has been associated with numerous comorbidities and decreased quality of life.³¹⁻³³ GSD is thought to have a complex etiology as well, and the role of the immune system in the development of gallstones has only been investigated recently. In vitro studies have shown that the presence of biliary immunoglobulins (Igs), particularly IgM, increases the nucleation of cholesterol crystals, although mouse studies have been more controversial.³⁴⁻³⁶ Inflammation has been shown to be a precursor to gallstone formation in both mouse and human studies,^{6,37} and is often accompanied by changes in gallbladder contractility and gallbladder epithelium transport ability.³⁷⁻³⁹ This appears to be secondary to impaired function of the prostaglandin-E₂ receptor, which has a cytoprotective function.⁴⁰ In the prairie dog model, inflammation was demonstrated to be an essential component in the development of GSD.⁴¹ Previous experiments in immune-deficient mice without T or B cells demonstrated that GSD in this study was secondary to a systemic proinflammatory Th1 immune response thought to be induced by cholesterol crystals.⁴²

It has also been thought that GSD may lead to an exacerbated inflammatory response.⁴³ Interestingly, a history of cholecystectomy-confirmed gallstones appeared to be more strongly associated with risk of developing both psoriasis and PsA than a history of symptomatic/radiographically-confirmed gallstones, suggesting that the severity of GSD may play a role in the linkage between gallstones and psoriasis. It is possible that the degree

of inflammation associated with GSD among the patients who underwent cholecystectomy was severe enough to trigger the development of psoriasis and PsA. Therefore, we speculate that the development of gallstone disease may contribute to the risk of psoriasis and PsA through involvement of the immune system and subsequent inflammatory pathways. As we found a stronger risk of psoriasis in patients with a baseline history of GSD, this suggests that there may be an underlying susceptibility in this patient population that increases their risks of both GSD and psoriasis. As the association was stronger in women with a BMI less than 30 kg/m², it may be worth further investigation to characterize the types of gallstones found as well.

In addition to a possible increased inflammatory state in participants with GSD, this susceptibility for both GSD and risk of psoriasis and PsA is likely due to shared risk factors for both conditions, such as diet and obesity. Patients with a history of cholecystectomy were more likely to have a higher BMI, exercise less, consume more alcohol, smoke, and have other comorbidities such as T2DM, hypertension, and hypercholesterolemia, which could mediate the risk for the development of psoriasis and PsA to an appreciable extent (Table 1). Nevertheless, the association between history of GSD and risk of psoriasis and PsA was still robust after adjustment for these factors. As an independent association was demonstrated, it is also possible that these patients may also share a common causal genetic predispositions for the development of these two disease processes, which is worthy of additional exploration in the future.

Limitations of this study include potential selection and information bias due to the retrospective characteristics of the study. However, our participants were all health care professionals, and their reports on both gallstones and psoriasis have been demonstrated to be highly accurate;²¹ confirmation of self-reported psoriasis has reached 92%.⁴⁴ Baseline characteristics of participants who responded to psoriasis questions was similar to those who did not respond,⁴⁵ so it is less likely that response bias would influence our results substantially. We also used history of cholecystectomy-confirmed gallstones to be a more accurate measure of whether patients had a true history of gallstones to reduce detection bias. Furthermore, as our study population was composed of mostly Caucasian women, the generalizability of our results may be limited, although both GSD and psoriasis are more common in women. Recently, some concern has been raised regarding possible misclassification of PsA cases by using the PASE questionnaire.⁴⁶ As the PASE questionnaire is more likely to pick up patients with active disease who are more likely to suffer from joint inflammation, it may underestimate the true number of patients with PsA. We sent out two waves of validation questionnaires to cohort participants who self-reported psoriasis, and asked the question “Has a rheumatologist ever diagnosed you with psoriatic arthritis?” in the second wave. Validation based on this question as well as other elements of the PASE questionnaire demonstrated a sensitivity of 77% and a specificity of 79%.^{24,46,47} Finally, we did not have specific information on type of gallstone, and it is unknown whether the association between history of GSD and risk of psoriasis and PsA may or may not be attributed to any specific gallstone type. Therefore, future studies are needed to explore this association of interest to a further extent.

In summary, the present study found that a personal history of GSD was associated with a significantly increased risk of psoriasis and PsA. Gallstones may be an important risk factor in the development of psoriasis, in which case this patient population could be under consideration to be screened more carefully for psoriasis and PsA. Further efforts are recommended to investigate the mechanisms behind the association between gallstones and psoriasis, and determine future clinical ramifications and potential treatment considerations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. *Gastroenterology*. Mar; 2009 136(3):741–754. [PubMed: 19166855]
2. Shaffer EA. Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? *Current gastroenterology reports*. May; 2005 7(2):132–140. [PubMed: 15802102]
3. Stinton LM, Myers RP, Shaffer EA. Epidemiology of gallstones. *Gastroenterology clinics of North America*. Jun; 2010 39(2):157–169. vii. [PubMed: 20478480]
4. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. *The American journal of gastroenterology*. Sep; 2006 101(9):2128–2138. [PubMed: 16848807]
5. Mendez-Sanchez N, Chavez-Tapia NC, Motola-Kuba D, et al. Metabolic syndrome as a risk factor for gallstone disease. *World journal of gastroenterology : WJG*. Mar 21; 2005 11(11):1653–1657. [PubMed: 15786544]
6. Rege RV, Prystowsky JB. Inflammation and a thickened mucus layer in mice with cholesterol gallstones. *The Journal of surgical research*. Jan; 1998 74(1):81–85. [PubMed: 9536979]
7. Zachariae H. Prevalence of joint disease in patients with psoriasis: implications for therapy. *American journal of clinical dermatology*. 2003; 4(7):441–447. [PubMed: 12814334]
8. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet*. Jul 21; 2007 370(9583):263–271. [PubMed: 17658397]
9. Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. *Nature*. Feb 22; 2007 445(7130):866–873. [PubMed: 17314973]
10. Horn EJ, Fox KM, Patel V, Chiou CF, Dann F, Lebwohl M. Are patients with psoriasis undertreated? Results of National Psoriasis Foundation survey. *J Am Acad Dermatol*. Dec; 2007 57(6):957–962. [PubMed: 17706322]
11. Gelfand JM, Gladman DD, Mease PJ, et al. Epidemiology of psoriatic arthritis in the population of the United States. *J Am Acad Dermatol*. Oct.2005 53(4):573. [PubMed: 16198775]
12. Augustin M, Reich K, Glaeske G, Schaefer I, Radtke M. Co-morbidity and age-related prevalence of psoriasis: analysis of health insurance data in Germany. *Acta Derm Venereol*. 2010; 90(2):147–151. [PubMed: 20169297]
13. Schon M, Boehncke W. Psoriasis. *N Engl J Med*. 2005; 352:1899–1912. [PubMed: 15872205]
14. Vena G, Vestita M, Cassano N. Psoriasis and cardiovascular disease. *Dermatol Ther*. 2010; 23:144–151. [PubMed: 20415821]

15. Shapiro J, Cohen A, David M. The association between psoriasis, diabetes mellitus, and atherosclerosis in Israel: a case-control study. *J Am Acad Dermatol.* 2007; 56:629–634. [PubMed: 17157411]
16. Gisondi P, Tessari G, Conti A, et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. *Br J Dermatol.* Jul; 2007 157(1):68–73. [PubMed: 17553036]
17. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. *Archives of internal medicine.* Aug 13-27; 2007 167(15):1670–1675. [PubMed: 17698691]
18. Carrascosa JM, Rocamora V, Fernandez-Torres RM, et al. Obesity and psoriasis: inflammatory nature of obesity, relationship between psoriasis and obesity, and therapeutic implications. *Actas dermo-sifilograficas.* Jan-Feb;2014 105(1):31–44. [PubMed: 23177976]
19. Chen LY, Qiao QH, Zhang SC, Chen YH, Chao GQ, Fang LZ. Metabolic syndrome and gallstone disease. *World journal of gastroenterology : WJG.* Aug 21; 2012 18(31):4215–4220. [PubMed: 22919256]
20. Taylor EN, Chan AT, Giovannucci EL, Curhan GC. Cholelithiasis and the risk of nephrolithiasis. *The Journal of urology.* Nov; 2011 186(5):1882–1887. [PubMed: 21944091]
21. Dominguez PL, Assarpour A, Kuo H, Holt EW, Tyler S, Qureshi AA. Development and pilot-testing of a psoriasis screening tool. *Br J Dermatol.* Oct; 2009 161(4):778–784. [PubMed: 19566664]
22. Husni ME, Meyer KH, Cohen DS, Mody E, Qureshi AA. The PASE questionnaire: pilot-testing a psoriatic arthritis screening and evaluation tool. *J Am Acad Dermatol.* Oct; 2007 57(4):581–587. [PubMed: 17610990]
23. Dominguez PL, Husni ME, Holt EW, Tyler S, Qureshi AA. Validity, reliability, and sensitivity-to-change properties of the psoriatic arthritis screening and evaluation questionnaire. *Archives of dermatological research.* Sep; 2009 301(8):573–579. [PubMed: 19603175]
24. Coates LC, Aslam T, Al Balushi F, et al. Comparison of three screening tools to detect psoriatic arthritis in patients with psoriasis (CONTEST study). *Br J Dermatol.* Apr; 2013 168(4):802–807. [PubMed: 23311587]
25. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *American journal of epidemiology.* May 15; 1992 135(10):1114–1126. discussion 1127–1136. [PubMed: 1632423]
26. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. *The Journal of investigative dermatology.* Jul; 2005 125(1):61–67. [PubMed: 15982303]
27. Torres T, Alexandre JM, Mendonca D, Vasconcelos C, Silva BM, Selores M. Levels of Physical Activity in Patients with Severe Psoriasis: A Cross-Sectional Questionnaire Study. *American journal of clinical dermatology.* Jan 24.2014
28. Schon MP, Boehncke WH. Psoriasis. *N Engl J Med.* May 5; 2005 352(18):1899–1912. [PubMed: 15872205]
29. Nickoloff BJ, Qin JZ, Nestle FO. Immunopathogenesis of psoriasis. *Clinical reviews in allergy & immunology.* Oct; 2007 33(1-2):45–56. [PubMed: 18094946]
30. Naldi L, Chatenoud L, Belloni A, et al. Medical history, drug exposure and the risk of psoriasis. Evidence from an Italian case-control study. *Dermatology.* 2008; 216(2):125–130. discussion 130-122. [PubMed: 18216474]
31. Armstrong AW, Schupp C, Wu J, Bebo B. Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation survey data 2003-2011. *PloS one.* 2012; 7(12):e52935. [PubMed: 23285231]
32. Grozdev I, Kast D, Cao L, et al. Physical and mental impact of psoriasis severity as measured by the compact Short Form-12 Health Survey (SF-12) quality of life tool. *The Journal of investigative dermatology.* Apr; 2012 132(4):1111–1116. [PubMed: 22205305]
33. Bhosle MJ, Kulkarni A, Feldman SR, Balkrishnan R. Quality of life in patients with psoriasis. Health and quality of life outcomes. 2006; 4:35. [PubMed: 16756666]

34. Harvey PR, Upadhyaya GA, Strasberg SM. Immunoglobulins as nucleating proteins in the gallbladder bile of patients with cholesterol gallstones. *The Journal of biological chemistry*. Jul 25; 1991 266(21):13996–14003. [PubMed: 1856228]
35. Harvey PR, Upadhyaya GA. A rapid, simple high capacity cholesterol crystal growth assay. *Journal of lipid research*. Sep; 1995 36(9):2054–2058. [PubMed: 8558092]
36. van Erpecum KJ, Wang DQ, Lammert F, Paigen B, Groen AK, Carey MC. Phenotypic characterization of Lith genes that determine susceptibility to cholesterol cholelithiasis in inbred mice: soluble pronucleating proteins in gallbladder and hepatic biles. *Journal of hepatology*. Oct; 2001 35(4):444–451. [PubMed: 11682027]
37. Hofmann AF. Pathogenesis of cholesterol gallstones. *Journal of clinical gastroenterology*. 1988; 10(Suppl 2):S1–11. [PubMed: 3062078]
38. Carey MC. Pathogenesis of gallstones. *American journal of surgery*. Apr; 1993 165(4):410–419. [PubMed: 8480873]
39. van Erpecum KJ, Wang DQ, Moschetta A, et al. Gallbladder histopathology during murine gallstone formation: relation to motility and concentrating function. *Journal of lipid research*. Jan; 2006 47(1):32–41. [PubMed: 16224116]
40. Xiao ZL, Amaral J, Biancani P, Behar J. Impaired cytoprotective function of muscle in human gallbladders with cholesterol stones. *American journal of physiology Gastrointestinal and liver physiology*. Mar; 2005 288(3):G525–532. [PubMed: 15486345]
41. Lee SP, Carey MC, LaMont JT. Aspirin prevention of cholesterol gallstone formation in prairie dogs. *Science*. Mar 27; 1981 211(4489):1429–1431. [PubMed: 7466399]
42. Maurer KJ, Rao VP, Ge Z, et al. T-cell function is critical for murine cholesterol gallstone formation. *Gastroenterology*. Oct; 2007 133(4):1304–1315. [PubMed: 17919501]
43. Nomura K, Mizutani H, Inachi S, Shimizu M. Remission of pustular psoriasis after cholecystectomy: role of focal infection in pustularization of psoriasis. *J Dermatol*. Feb; 1995 22(2):122–124. [PubMed: 7722087]
44. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *American journal of epidemiology*. May; 1986 123(5):894–900. [PubMed: 3962971]
45. Li W, Han J, Hu FB, Curhan GC, Qureshi AA. Psoriasis and risk of type 2 diabetes among women and men in the United States: a population-based cohort study. *The Journal of investigative dermatology*. Feb; 2012 132(2):291–298. [PubMed: 21993559]
46. Wu S, Li WQ, Han J, Sun Q, Qureshi AA. Hypercholesterolemia and Risk of Incident Psoriasis and Psoriatic Arthritis in US Women. *Arthritis and rheumatism*. Dec 18.2013
47. Haroon M, Kirby B, FitzGerald O. High prevalence of psoriatic arthritis in patients with severe psoriasis with suboptimal performance of screening questionnaires. *Annals of the rheumatic diseases*. May; 2013 72(5):736–740. [PubMed: 22730367]

What is already known about this topic?

- Psoriasis, a debilitating chronic disease, may share some common risk factors and thus etiologic pathways with gallstones.
- To date, the association between gallstones and psoriasis has not yet been investigated.

What does this study add?

- A history of cholecystectomy-confirmed gallstones was associated with a higher relative risk of developing both psoriasis and psoriatic arthritis.
- A history of gallstones was associated with increased risk of developing concomitant psoriatic arthritis, especially in patients with a BMI under 30 kg/m².

Table 1
Age-standardized characteristics of the Nurses' Health Study II population at baseline (1991) by history of cholecystectomy

	No history of cholecystectomy (n = 87,024)	Cholecystectomy (n = 2,206)	P value
Age, yrs	36.14 (4.65)	37.79 (4.48)	<0.001
Body mass index	24.45 (5.15)	29.07 (7.31)	<0.001
Total activity mets/wk	20.83 (26.75)	18.47 (24.75)	<0.001
Alcohol gm/d	3.16 (6.09)	2.02 (5.08)	<0.001
Current smoker, %	11.22	14.46	<0.001
Past smoker, %	22.44	19.18	0.18
CVD, %	0.03	0.03	0.56
T2DM, %	0.12	0.69	<0.001
Hypertension, %	5.96	18.18	<0.001
Hypercholesterolemia, %	14.29	26.73	<0.001
White, %	95.51	95.89	0.36

Values (except age) are means (SD) or percentages and are standardized to the age distribution of the study population.

Table 2
The association of a history of gallstones with risk of psoriasis in the Nurses' Health Study II population

	No. of psoriasis cases/person-years	Age-adjusted RR	Multivariate-adjusted RR ^a	Multivariate-adjusted RR ^b
Updated				
No cholecystectomy	571/1,152,955	1.00	1.00	1.00
Cholecystectomy	71/80,087	1.55 (1.21, 2.00)	1.53 (1.19, 1.96)	1.22 (0.95, 1.58)
No history of gallstones	565/1,136,172	1.00	1.00	1.00
Symptomatic or radiographic gallstones	77/96,870	1.41 (1.11, 1.80)	1.38 (1.08, 1.75)	1.10 (0.86, 1.41)
Baseline (1991)				
No cholecystectomy	607/1,207,731	1.00	1.00	1.00
Cholecystectomy	35/30,311	2.22 (1.58, 3.13)	2.20 (1.56, 3.10)	1.70 (1.20, 2.41)
No history of gallstones	593/1,180,387	1.00	1.00	1.00
Symptomatic or radiographic gallstones	49/52,654	1.80 (1.34, 2.41)	1.75 (1.30, 2.35)	1.36 (1.01, 1.84)

^a Multivariate-adjusted analyses controlling for age, smoking status (never, past, current 1-14 cigs/day, 15-24 cigs/day and 25+ cigs/day), exercise (as quintiles), alcohol consumption (none, 0.1-4.9 g/d, 5.0-9.9 g/d, 10+ g/d), ethnicity (white, Asian, Hispanic and African American).

^b Additionally adjusted for body mass index as a continuous variable.

Table 3
The association of a history of gallstones with risk of psoriatic arthritis (PsA) in the Nurses' Health Study II population

	No. of PsA cases/ person-years	Age-adjusted RR	Multivariate-adjusted RR ^a	Multivariate-adjusted RR ^b
Updated				
No cholecystectomy	122/1,152,955	1.00	1.00	1.00
Cholecystectomy	35/80,087	3.45 (2.34, 5.08)	3.07 (2.08, 4.55)	2.21 (1.48, 3.29)
No history of gallstones	125/1,136,172	1.00	1.00	1.00
Symptomatic or radiographic gallstones	32/96,870	2.51 (1.69, 3.73)	2.21 (1.48, 3.29)	1.55 (1.03, 2.34)
Baseline (1991)				
No cholecystectomy	138/1,202,731	1.00	1.00	1.00
Cholecystectomy	19/30,311	5.00 (3.09, 8.11)	4.41 (2.70, 7.18)	2.96 (1.80, 4.89)
No history of gallstones	137/1,180,387	1.00	1.00	1.00
Symptomatic or radiographic gallstones	20/52,654	2.96 (1.84, 4.75)	2.55 (1.58, 4.12)	1.70 (1.04, 2.78)

^a Multivariate-adjusted analyses controlling for age, smoking status (never, past, current 1-14 cigs/day, 15-24 cigs/day and 25+ cigs/day), exercise (as quintiles), alcohol consumption (none, 0.1-4.9 g/d, 5.0-9.9 g/d, 10+ g/d), and ethnicity (white, Asian, Hispanic and African American).

^b Additionally adjusted for body mass index as a continuous variable.

Table 4
The association between an updated history of cholecystectomy-confirmed gallstones with risk of PsA according to status of obesity in the Nurses' Health Study II

BMI <30kg/m²		BMI ≥ 30 kg/m²	
No. of PsA cases/person-years	Multivariate-adjusted RR	No. of PsA cases/ person-years	Multivariate-adjusted RR
No 66/947,151	1.00	56/205,804	1.00
Yes 13/41,776	3.18 (1.71, 5.90)	22/38,311	1.72 (1.04, 2.85)

Multivariate-adjusted analyses controlling for age, smoking status (never, past, current 1-14 cigs/day, 15-24 cigs/day and 25+ cigs/day), exercise (as quintiles), alcohol consumption (none, 0.1-4.9 g/d, 5.0-9.9 g/d, 10+ g/d), ethnicity (white and nonwhite) and body mass index (continuous). *P* for interaction = 0.02.