Association between Alcohol Consumption and Diverticulosis and Diverticular Bleeding: A Systematic Review and Meta-analysis

Veeravich Jaruvongvanich MD; Anawin Sanguankeo MD; and Sikarin Upala MD, MS

Abstract

There have been conflicting reports on the association of alcohol use and diverticular disease. We aimed to determine the odds of developing diverticular disease and diverticular bleeding in patients who consumed alcohol on a regular basis compared with those who did not. MEDLINE and PUBMED were searched up until February 2017 on observational trials, which investigated the effect of alcohol use on two outcomes of diverticular disease: diverticulosis and diverticular bleeding. Quantitative estimates (odds ratios [OR] and confidence intervals [CI]) from included studies were pooled by using a random-effects model. Heterogeneity across studies was assessed by the I^2 statistic. In 6 studies including 53,644 subjects and 6 studies including 3,404 subjects, alcohol consumption on a regular basis was not associated with either diverticulosis (OR=1.99; 95% CI 0.99-4.03, I^2=99%) or diverticular bleeding (OR=1.39; 95% CI 0.84-2.32, I^2=45%) compared to subjects who did not consume alcohol on a regular basis, respectively. Increased odds of diverticulosis or diverticular bleeding among individuals who consume alcohol on a regular basis were not observed in these meta-analyses.

Keywords

Alcohol; Diverticulosis; Diverticular bleeding; Meta-analysis

Introduction

Diverticulosis is one of the leading causes of outpatient clinic visits and inpatient admissions for gastrointestinal disorders in the United States.[1] It represents the fifth most expensive gastrointestinal disease in the United States in terms of direct and indirect costs ($2.5 billion per year) with an associated annual mortality of 2.5 per 100,000 persons.[2] Prevalence appears to be higher in the United States and Europe compared to Asia and Africa.[3] Nevertheless, the number of individuals with diverticulosis in lower prevalence areas is increasing due to westernization. Risk factors for diverticulosis apart from age and obesity remain uncertain.[4-6] While eighty percent of persons with diverticulosis remain asymptomatic throughout their lifetime, the remainder may develop severe complications such as diverticulitis, abscess formation, perforation, and fistulation.[7] Since diverticulosis can progress into serious complications, identifying the modifiable risk factors for diverticula formation is essential in order to prevent those lethal consequences. Diverticular bleeding is one of the most frequent complications accounting for 40% of lower gastrointestinal hemorrhage.[8] Identifiable risks of diverticular bleeding include age, obesity, the use of NSIADs and aspirin, and arteriosclerotic diseases.[9-12]

Alcohol is the most commonly used and abused drug throughout the world.[13] In 2015, 51.8% of adults 18 years and older in Hawai'i drank at least one alcoholic beverage within the past 30 days, and 7.7% were considered heavy drinkers (defined as men having >2 drinks per day, women having >1 drink per day).[14] Alcohol has several pathologic effects on the gastrointestinal tract. It can cause mucosal injury, impair motility, and inhibit the absorption of nutrients, resulting in various gastrointestinal disorders including esophagitis, gastritis, malabsorption syndrome, and gastrointestinal tumors.[15,16] Furthermore, it is associated with reduced rectosigmoid motility that is thought to be an important pathogenic factor of diverticula formation. Some previous studies showed that consuming alcohol was related to increased odds of diverticulosis[17-20] and diverticular bleeding.[11] By contrast, these associations were not observed in some studies.[21-26] Therefore, we carried out a comprehensive meta-analysis to investigate the association between alcohol consumption and both diverticulosis and diverticular bleeding.

Materials and Methods

Search Strategy

We registered our meta-analysis in PROSPERO (registration number: CRD42016032851). Two reviewers performed a systematic search in PubMed and EMBASE from inception to February 2017 independently using the search terms that comprised alcohol and diverticulosis, as detailed in Item S1, with no restriction in language. Manual searches of reference lists from retrieved articles and review articles were also performed.

Eligibility Criteria

All published observational studies that investigated the association between alcohol intake and diverticulosis and diverticular bleeding in adult participants were included. Cases were participants with higher alcohol consumption, whereas controls were participants with lower alcohol consumption. Higher and lower alcohol consumption thresholds were defined by each study. Diverticulosis was ascertained by imaging studies including computed tomography, barium enema, or colonoscopy. We excluded reviews, letters to the editor, editorials, and conference abstracts.

Data Extraction

The following data were recorded from each study: first author, publication year, sample size, study design, participant characteristics, definition of alcohol use in cases and controls. The Newcastle–Ottawa Scale (NOS) was utilized to assess the methodological quality of included studies that is based on selection of study groups, comparability of study groups, and the ascertainment of the exposure/outcome of interest.[27] Two reviewers independently extracted the data. Differences were solved by discussion between the authors. We conducted 2 meta-analyses, one where the outcome is diverticulosis and one where the outcome is diverticular bleeding. Each meta-analysis derived from each set of manuscripts.

Statistical Analysis

Generic inverse variance based on calculating odds ratios (OR) of the association between alcohol consumption and diverticulosis and diverticular bleeding and standard errors comparing between subjects who consumed alcohol on a regular basis to those who did not was conducted using a random-effects model. We used estimates that adjusted to the highest degree of confounders if the study provided more than one multivariable adjusted estimate. The between-study heterogeneity was tested with use of both Q and I^2 statistic values. An I^2 of more than 50% indicates substantial heterogeneity.[28] We performed sensitivity analyses by eliminating one study at a time to confirm the robustness of the result. A funnel plot is a scatterplot of outcome (vertical axis) and study size (horizontal axis). Visual inspection for asymmetry of funnel plots was performed to assess publication bias.[29] Formal statistical assessment of funnel plot asymmetry was done with Egger's regression test.[30] $P < .1$ was considered statistically significant. Comprehensive Meta-Analysis 3.3 was used for data analysis.

Results

The database search resulted in 156 articles but only 134 remained after duplicates were removed. Of these, 115 articles were eliminated after reviewing titles and abstracts. We reviewed the full text for the remaining 19 articles. Seven articles were further removed because they were duplicate publications (2 articles), had no outcome of interest (2 article), had no subject of interest (2 articles), or had no control group (1 article). The final analysis includes 6 articles [17-21,24] for diverticulosis and 6 articles [18,22,23,25,26,31] for diverticular bleeding. Table 1 and Table 2 show the main characteristics of the trials for diverticulosis and diverticular bleeding, respectively. Item S2 demonstrates the search methodology.

The Odds of Diverticulosis in Patients Consuming Alcohol

Six observational studies (5 cross-sectional studies[17-21] and 1 cohort study[24]) involving 53,644 participants were analyzed for diverticulosis. The pooled OR of diverticulosis in subjects with higher alcohol consumption was 1.99 (95% CI 0.99-4.03) compared to those with lower alcohol consumption (Figure 1). The statistical between-study heterogeneity (I^2) was 94% with $P_{heterogeneity}$ of less than 0.01. The sensitivity analysis confirmed the robustness of the findings (Item S3). The funnel plot excluded bias with non-significant Egger's test (P = 0.20) (Item S4).

The Odds of Diverticular Bleeding in Patients Consuming Alcohol

Six observational studies (3 cross-sectional studies[11,23,26] and 3 case-control studies[22,25,31]) involving 3,404 participants were analyzed for diverticular bleeding (Figure 2). The pooled OR of diverticular bleeding in subjects with higher alcohol consumption was 1.39 (95% CI 0.84-2.32) compared to those with lower alcohol consumption. The statistical between-study heterogeneity (I^2) was 45% with $P_{heterogeneity}$ of 0.001. Sensitivity analysis further confirmed the robustness of the findings (Item S5). The funnel plot excluded bias with non-significant Egger's test (P = 0.99) (Item S6).

Discussion

Alcohol has been widely used across the world and has been related to multiple gastrointestinal disorders. Several studies have reported inconsistent results regarding the association of alcohol consumption and diverticulosis and diverticular bleeding. Our meta-analyses found no association between alcohol use and diverticulosis or diverticular bleeding.

However, significantly increased risk of diverticulosis in alcohol drinkers was reported by several previous studies.[17-20] The exact mechanism is unknown, but the plausible explanation is due to increased intra-colonic pressure secondary to impaired colonic motility from alcohol.[32,33] This classical pathophysiologic concept of diverticula formation needs to be reconsidered. Painter, et al, first proposed the pathogenesis of diverticulosis in 1969 to be the relation between eating habits and geographical distribution of this disorder.[34] It was thought that a low-fiber diet created an excessive segmental contraction in the colon that further increases intraluminal pressure and facilitates mucosal herniation. Excessive contraction of the colon was due to increased water reabsorption secondary to low-residue diet, leading to smaller colonic luminal diameter and increased colonic pressure.[35] This hypothesis was further argued by a number of following studies. Peery, et al, performed a cross-sectional study involving more than 2,000 subjects showing that both constipation and a low-fiber diet were not associated with an increased risk of diverticulosis.[36] Another large population-based study from Austria also showed no association between constipation and diverticulosis.[37] Bottner, et al, proposed an alternative pathogenic hypothesis that an enteric neuropathy and myopathy may underlie the development of diverticulosis.[38] Based on this available evidence, our finding shows no increased odds of diverticulosis in alcohol drinkers and does not support the Painter hypothesis.

Additionally, there are few studies assessing alcohol consumption and the risk of diverticular bleeding. Nagata, et al, conducted a prospective study including 911 patients with diverticulosis showing increased odds of bleeding in moderate drinkers compared to non-drinkers.[11] A possible mechanism could be mucosal irritation similar to the effect of esophagitis and gastritis.[39] After summarization of all included studies, we found no association between alcohol drinkers and diverticular bleeding.

It should be noted that our negative results should be interpreted with caution because high between-study heterogeneity was observed in our meta-analysis that could be from variability in participants' characteristics, interventions, and study designs. Sensitivity analyses were performed to confirm that no single study significantly altered the summary of our findings.

There are some limitations that should be acknowledged. First, we could not report a causal association between alcohol consumption and diverticulosis given the nature of these observational studies. Second, high between-study heterogeneity was observed in this study, which indicates high variation in study outcomes between studies, therefore our result needs to be interpreted with caution. Third, we could not carry out a subgroup analysis according to age, sex, fiber intake, smoking, and BMI since these were not provided in the primary studies. These variables are potential confounders that could interfere with this association. Fourth, not all included effect estimates were adjusted for these potential confounders; this could affect the validity of our results. Fifth, some of the included studies did not report the definition of alcohol drinkers regarding the amount of alcohol consumption. Sixth, most of the included studies are from Asia that may limit the generalizability our findings. Finally, only 12 studies were included in the analysis of diverticulosis and diverticular bleeding.

In summary, significantly increased odds of diverticulosis and diverticular bleeding among individuals who consumed alcohol were not observed in this meta-analysis. Further randomized controlled trials are required to better clarify this association.

Table 1. Characteristics of Included Studies of the Odds of Diverticulosis

	Sakuta, et al[21]	Song, et al[17]	Crowe, et al[24]	Nagata, et al[18]	Sharara, et al[19]	Wang, et al[20]
Country	Japan	Korea	United Kingdom	Japan	Lebanon	Taiwan
Year	2007	2010	2011	2013	2013	2015
Study design	Cross-sectional	Cross-sectional	Prospective cohort study	Cross-sectional	Cross-sectional	Cross-sectional
Total number	954	848	47,033	2,164	746	1,899
Alcoholic use in case	Alcohol ≥ 30 ml per day	N/A	Alcohol ≥ 16 grams per day	Alcohol ≥ 360 gm per week	Alcohol ≥ 1 drink per day	Alcohol > 3 times per week
Alcoholic use in control	Alcohol < 30 ml per day	Non-drinker	1-7 grams per day	Non-drinker	Non-drinker	≤ 3 times per week
Mean age (years)	53.0±1.2	50.9 ± 12.3	N/A	N/A	61.1 ± 8.3	52.8 ± 10.6
Female (%)	0	38.9	75.9	37	50.5	36.7
Confounder adjustment	N/A	Age, sex, BMI, smoking, mini dietary assessment index, diabetes, and hypertension	Smoking	Age, sex, smoking, aspirin use, anticoagulants, corticosteroid, hypertension, and atherosclerotic disease	Age, sex, BMI, bowel movement frequency, exercise, aspirin, and adenoma	Age, sex, smoking, colonic polyps
Quality assessment (NOS: selection, comparability, outcome)	3,0,3	3,2,3	3,1,3	4,2,3	4,2,3	3,2,3

Abbreviations: BMI: Body mass index; HTN: Hypertension; NOS: Newcastle Ottawa scale

Table 2. Characteristics of Included Studies of the Odds of Diverticular Bleeding

	Sugihara, et al[31]	Suh, et al[26]	Jansen, et al[23]	Nagata, et al[11]	Tsuruoka, et al[25]	Yamada, et al[22]
Country	Japan	Korea	Germany	Japan	Japan	Japan
Year	2016	2012	2009	2014	2011	2008
Study design	CC	CS	CS	CS	CC	CC
Total number	221	216	140	911	163	1,753
Alcoholic use in case	Beer ≥ 350 mL per day	N/A	N/A	Alcohol ≥ 180 grams per week	N/A	Alcohol ≥ 20 grams per day
Alcoholic use in control	Beer < 350 mL per day	Non-drinker	Non-drinker	Non-drinker	Non-drinker	Non-drinker
Mean age (years)	70 (33–92)	65.9±13.7	73.4 ± 9.9	66 ± 12	69	67.2±12.8
Female (%)	35.7	43.1	60	34	31.4	27.4
Confounder adjustment	N/A	N/A	N/A	Age, sex, smoking, aspirin, NSAIDs, acetaminophen, anticoagulants, corticosteroid use, Charlson comorbidity index, gastrointestinal symptoms score	N/A	N/A
Quality assessment (NOS: selection, comparability, outcome)	4,0,2	3,0,3	4,1,3	4,2,3	3,0,3	4,2,3

Abbreviation: CC: case-control study; CS: cross-sectional study; NSAIDs: non-steroidal anti-inflammatory drugs; NOS: Newcastle Ottawa scale

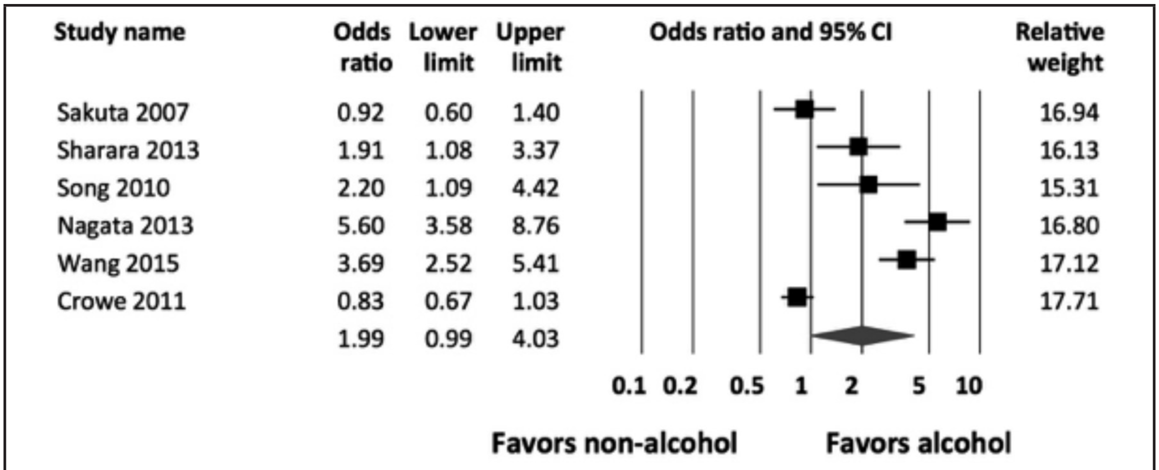


Figure 1. Forest plot of the included studies with adjusted analysis assessing odds of diverticulosis in individuals who consumed alcohol, square data markers represent ORs; horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall OR and 95% CI for the outcome of interest.

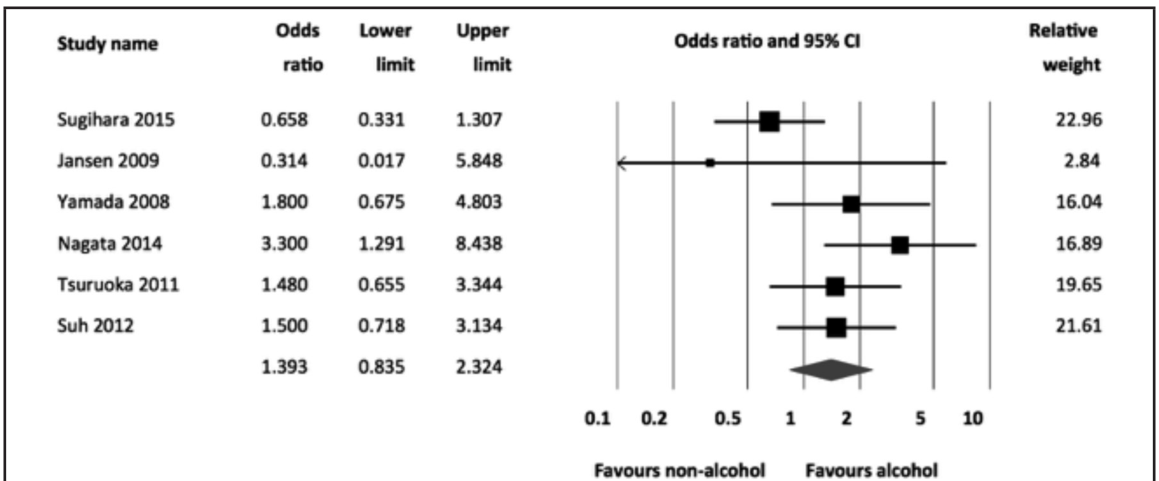


Figure 2. Forest plot of the included studies with adjusted analysis assessing odds of diverticular bleeding in individuals who consumed alcohol, square data markers represent ORs; horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall OR and 95% CI for the outcome of interest.

MEDLINE

1 diverticulosis.mp. or exp Diverticulum/

2 diverticular.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

3 colon diverticulum.mp. or exp Diverticulum, Colon/

4 exp Colon/

5 (colon or colonic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

6 4 or 5

7 1 or 2

8 6 and 7

9 3 or 8

10 Ethanol.mp. or exp Ethanol/

11 exp Alcohols/

12 Alcohol*.mp.

13 grain alcohol.mp.

14 ethyl alcohol.mp.

15 alcoholic beverages.mp.

16 beer.mp.

17 wine.mp.

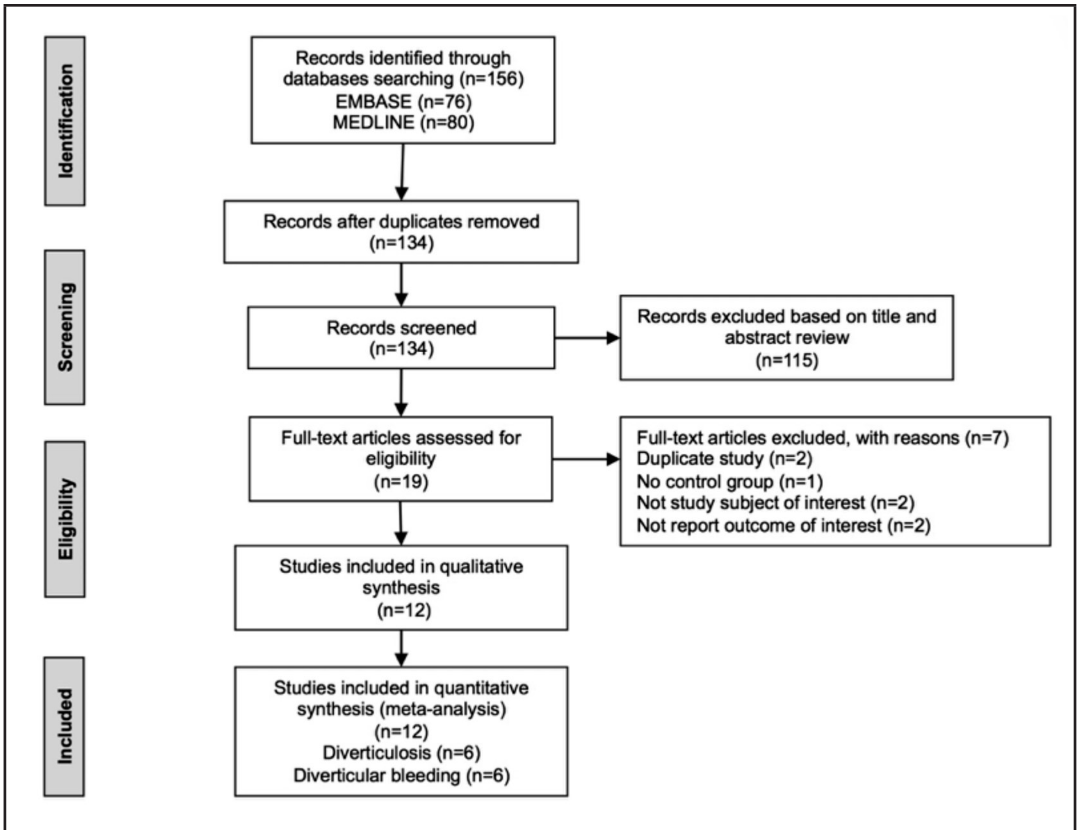
18 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19 9 and 18

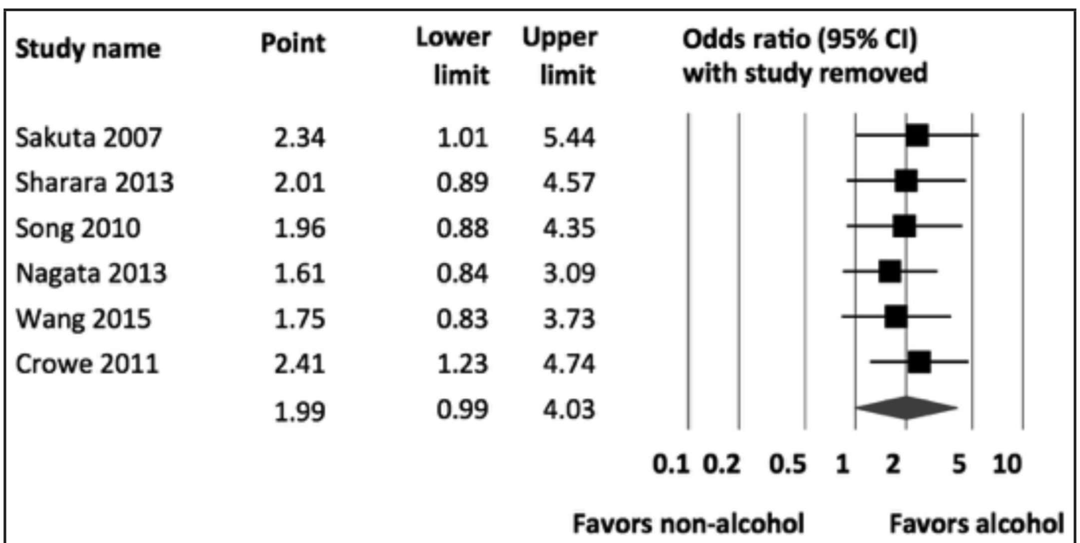
EMBASE

((('colon diverticulum'/exp or 'colon diverticulum') or (((colon or colonic) or 'colon'/exp) and (('diverticulosis'/exp or 'diverticulosis') or diverticular))) and (('alcohol'/exp or 'alcohol') or ethanol or (ethyl and alcohol) or ('alcoholic

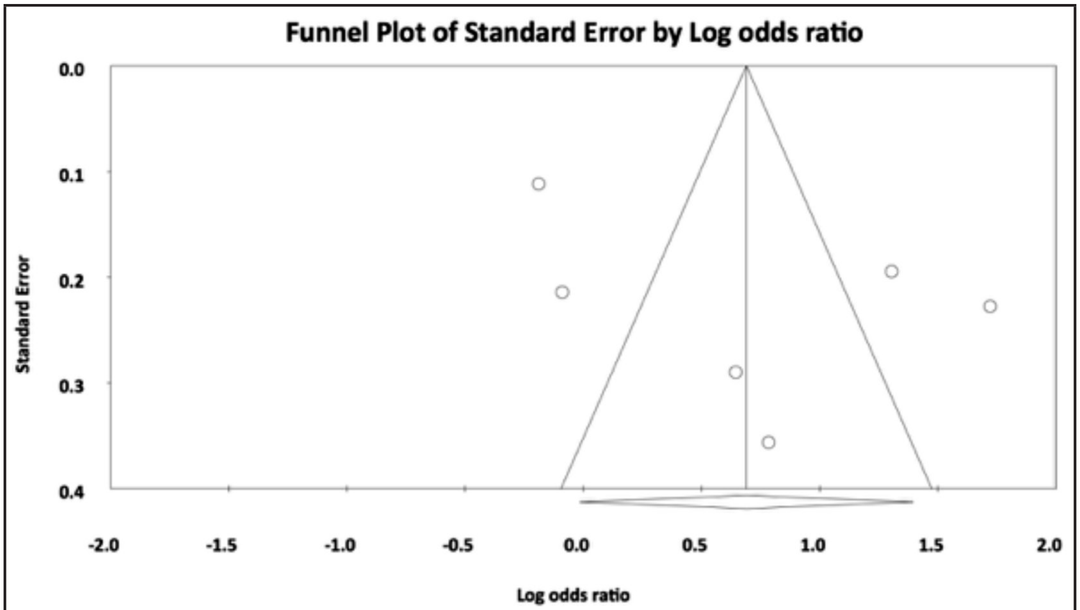
Supplementary Material
Item S1. Search Strategy



Supplementary Material
Item S2. Search Methodology and Selection Process

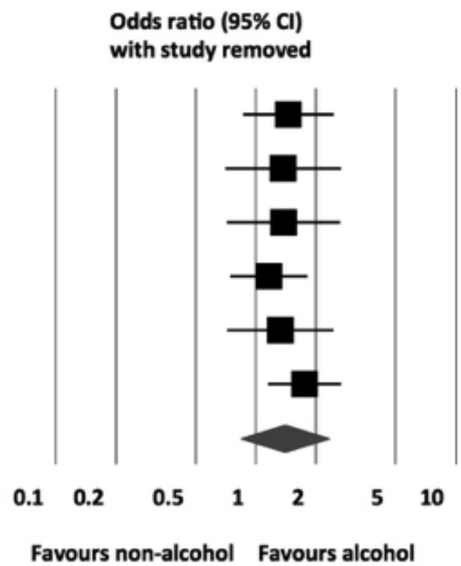


Supplementary Material
Item S3. Sensitivity analysis for the influence of individual studies on the pooled estimate for assessing the odds of diverticulosis as determined by the leave-one-out method. CI, confidence interval.

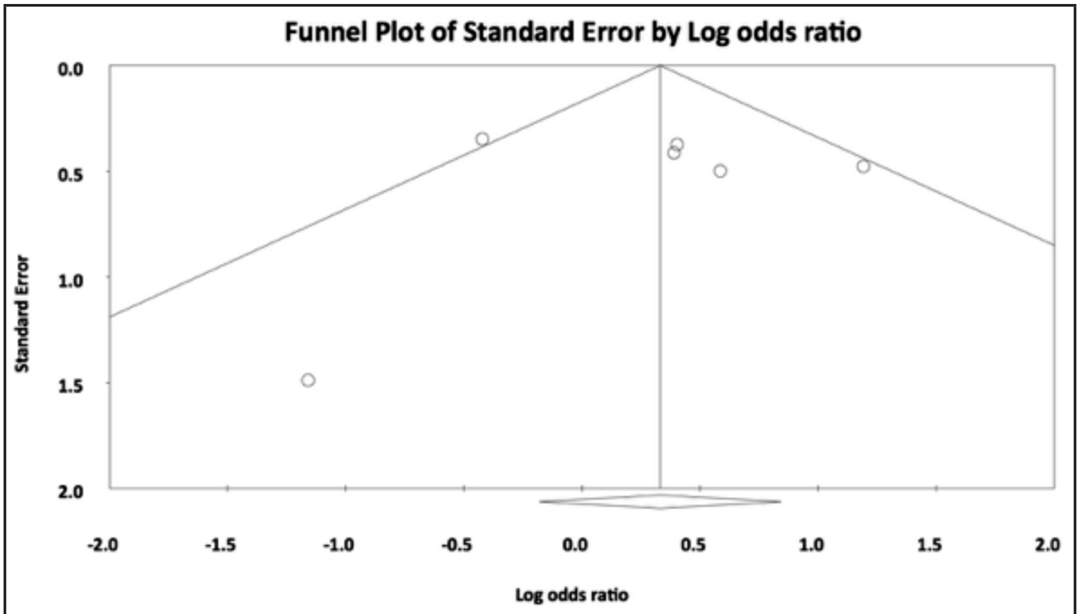


Supplementary Material
Item S4. Funnel plot of the included studies comparing odds of diverticulosis in patients who consumed alcohol on a regular basis and those who did not; A diamond data marker represents the overall odds ratios and 95% CI for the outcome of interest.

Study name	Point	Lower limit	Upper limit
Jansen 2009	1.457	0.863	2.458
Suh 2012	1.370	0.703	2.670
Tsuruoka 2011	1.377	0.717	2.644
Nagata 2014	1.163	0.743	1.819
Yamada 2008	1.328	0.720	2.451
Sugihara 2015	1.754	1.151	2.672
	1.393	0.835	2.324



Supplementary Material
Item S5. Sensitivity analysis for the influence of individual studies on the pooled estimate for assessing the odds of diverticular bleeding as determined by the leave-one-out method. CI, confidence interval.



Supplementary Material
Item S6. Funnel plot of the included studies comparing odds of diverticular bleeding in patients who consumed alcohol on a regular basis and those who did not; A diamond data marker represents the overall odds ratios and 95% CI for the outcome of interest.

Conflict of Interest

None of the authors identify a conflict of interest.

Acknowledgements

We thank Matthew Roslund for validation of the search. This study was registered in PROSPERO (registration number: CRD42016032851).

Author Affiliations:
- Department of Internal Medicine, University of Hawai'i, Honolulu, HI (VJ)
- Department of Internal Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand (VJ)
- Department of Internal Medicine, Bassett Medical Center and Columbia University College of Physicians and Surgeons, Cooperstown, NY (AS, SU)
- Department of Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand (AS, SU)

Correspondence to:
Veeravich Jaruvongvanich MD; 1511 Nuuanu ave, Honolulu, HI 96817;
Email: veeravich_j@hotmail.com

Reference

1. 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.
2. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. *Gastroenterology.* May 2002;122(5):1500-1511.
3. Painter NS, Burkitt DP. Diverticular disease of the colon: a deficiency disease of Western civilization. *British Medical Journal.* May 22 1971;2(5759):450-454.
4. Nagata N, Sakamoto K, Arai T, et al. Visceral Abdominal Obesity Measured by Computed Tomography is Associated With Increased Risk of Colonic Diverticulosis. *Journal of Clinical Gastroenterology.* Nov-Dec 2015;49(10):816-822.
5. Dore MP, Pes GM, Marras G, et al. Risk factors associated with colonic diverticulosis among patients from a defined geographic area. *Techniques in Coloproctology.* Mar 2016;20(3):177-183.
6. Parks TG. Natural history of diverticular disease of the colon. *Clinics in Gastroenterology.* Jan 1975;4(1):53-69.
7. Stollman N, Raskin JB. Diverticular disease of the colon. *Lancet.* Feb 21 2004;363(9409):631-639.
8. Longstreth GF. Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: a population-based study. *The American Journal of Gastroenterology.* Mar 1997;92(3):419-424.
9. Strate LL, Liu YL, Huang ES, Giovannucci EL, Chan AT. Use of aspirin or nonsteroidal anti-inflammatory drugs increases risk for diverticulitis and diverticular bleeding. *Gastroenterology.* May 2011;140(5):1427-1433.
10. Okamoto T, Watabe H, Yamada A, Hirata Y, Yoshida H, Koike K. The association between arteriosclerosis related diseases and diverticular bleeding. *International Journal of Colorectal Disease.* Sep 2012;27(9):1161-1166.
11. Nagata N, Niikura R, Aoki T, et al. Colonic diverticular hemorrhage associated with the use of nonsteroidal anti-inflammatory drugs, low-dose aspirin, antiplatelet drugs, and dual therapy. *Journal of Gastroenterology and Hepatology.* Oct 2014;29(10):1786-1793.
12. Nagata N, Sakamoto K, Arai T, et al. Visceral fat accumulation affects risk of colonic diverticular hemorrhage. *International Journal of Colorectal Disease.* Oct 2015;30(10):1399-1406.
13. Lieber CS. Medical disorders of alcoholism. *The New England Journal of Medicine.* Oct 19 1995;333(16):1058-1065.
14. “Hawaii State Department of Health HHDWBRFSSRoM, 2017 from Hawaii State Department of Health,Hawaii Health Data Warehouse Indicator-Based Information System for Public Health website: http://ibis.hhdw.org/ibisph-view/. http://ibis.hhdw.org/ibisph-view/.
15. Bujanda L. The effects of alcohol consumption upon the gastrointestinal tract. *The American Journal of Gastroenterology.* Dec 2000;95(12):3374-3382.
16. Stermer E. Alcohol consumption and the gastrointestinal tract. *The Israel Medical Association Journal : IMAJ.* Mar 2002;4(3):200-202.
17. Song JH, Kim YS, Lee JH, et al. Clinical characteristics of colonic diverticulosis in Korea: a prospective study. *The Korean Journal of Internal Medicine.* Jun 2010;25(2):140-146.
18. Nagata N, Niikura R, Shimbo T, et al. Alcohol and smoking affect risk of uncomplicated colonic diverticulosis in Japan. *PloS one.* 2013;8(12):e81137.
19. Sharara AI, El-Halabi MM, Mansour NM, et al. Alcohol consumption is a risk factor for colonic diverticulosis. *Journal of Clinical Gastroenterology.* May-Jun 2013;47(5):420-425.
20. Wang FW, Chuang HY, Tu MS, et al. Prevalence and risk factors of asymptomatic colorectal diverticulosis in Taiwan. *BMC Gastroenterology.* 2015;15:40.
21. Sakuta H, Suzuki T. Prevalence rates of type 2 diabetes and hypertension are elevated among middle-aged Japanese men with colonic diverticulum. *Environmental Health and Preventive Medicine.* Mar 2007;12(2):97-100.
22. Yamada A, Sugimoto T, Kondo S, et al. Assessment of the risk factors for colonic diverticular hemorrhage. *Diseases of the Colon and Rectum.* Jan 2008;51(1):116-120.
23. Jansen A, Harenberg S, Grenda U, Elsing C. Risk factors for colonic diverticular bleeding: a Westernized community based hospital study. *World Journal of Gastroenterology.* Jan 28 2009;15(4):457-461.

24. Crowe FL, Appleby PN, Allen NE, Key TJ. Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. *BMJ.* 2011;343:d4131.
25. Tsuruoka N, Iwakiri R, Hara M, et al. NSAIDs are a significant risk factor for colonic diverticular hemorrhage in elder patients: evaluation by a case-control study. *Journal of Gastroenterology and Hepatology.* Jun 2011;26(6):1047-1052.
26. Suh S, Seo PJ, Park H, et al. [The risk factors for colonic diverticular bleeding]. *The Korean Journal of Gastroenterology = Taehan Sohwagi Hakhoe chi.* Dec 2012;60(6):349-354.
27. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology.* Sep 2010;25(9):603-605.
28. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* Sep 6 2003;327(7414):557-560.
29. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *Journal of Clinical Epidemiology.* Oct 2001;54(10):1046-1055.
30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* Sep 13 1997;315(7109):629-634.
31. Sugihara Y, Kudo SE, Miyachi H, et al. Analysis of Risk Factors for Colonic Diverticular Bleeding: A Matched Case-Control Study. *Gut and Liver.* Jun 19 2015.
32. Berenson MM, Avner DL. Alcohol inhibition of rectosigmoid motility in humans. *Digestion.* 1981;22(4):210-215.
33. Bouchoucha M, Nalpas B, Berger M, Cugnenc PH, Barbier JP. Recovery from disturbed colonic transit time after alcohol withdrawal. *Diseases of the Colon and Rectum.* Feb 1991;34(2):111-114.
34. Painter NS. Diverticular disease of the colon--a disease of the century. *Lancet.* Sep 13 1969;2(7620):586-588.
35. Painter NS, Burkitt DP. Diverticular disease of the colon, a 20th century problem. *Clinics in Gastroenterology.* Jan 1975;4(1):3-21.
36. Peery AF, Sandler RS, Ahnen DJ, et al. Constipation and a low-fiber diet are not associated with diverticulosis. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association.* Dec 2013;11(12):1622-1627.
37. Braunschmid T, Stift A, Mittlbock M, Lord A, Weiser FA, Riss S. Constipation is not associated with diverticular disease - Analysis of 976 patients. *International Journal of Surgery.* Jul 2015;19:42-45.
38. Bottner M, Wedel T. Abnormalities of neuromuscular anatomy in diverticular disease. *Digestive Diseases.* 2012;30(1):19-23.
39. Chen SH, Wang JW, Li YM. Is alcohol consumption associated with gastroesophageal reflux disease? *Journal of Zhejiang University. Science. B.* Jun 2010;11(6):423-428.