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CLINICAL—ALIMENTARY TRACT

Nonsteroidal Anti-inflammatory Drug Use Reduces Risk of Adenocarcinomas of the Esophagus and Esophagogastric Junction in a Pooled Analysis

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This article has an accompanying continuing medical education activity on page e22. Learning Objective: Upon completion of this assessment, successful learners will be able to understand the epidemiological evidence supporting the association between NSAID use and esophageal adenocarcinoma.

BACKGROUND & AIMS: Regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been reported to reduce risks of esophageal adenocarcinoma (EAC) and esophagogastric junctional adenocarcinoma (EGJA). However, individual studies have been too small to accurately assess the effects of medication type, frequency, or duration of use. We performed a pooled analysis to investigate these associations. **METHODS:** We performed a pooled analysis of 6 population-based studies within the Barrett's and Esophageal Adenocarcinoma Consortium to evaluate the association between NSAID use and the risk of EAC and EGJA, using uniform exposure definitions. We collected information from 6 studies (5 case-control and 1 cohort), with a total of 1226 EAC and 1140 EGJA cases, on aspirin and/or NSAID use. Study-specific odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariate adjusted logistic regression models and then pooled using a random effects meta-analysis model. **RESULTS:** Compared with nonusers, individuals who have used NSAIDs had a statistically significant reduced risk of EAC (OR, 0.68; 95% CI, 0.56–0.83); they also appeared to have a reduced risk of EGJA (OR, 0.83; 95% CI, 0.66–1.03). Similar reductions in risk were observed among individuals who took aspirin or nonaspirin NSAIDs. The highest levels of frequency (daily or more frequently) and duration (≥10 years) of NSAID use were associated with an approximately 40% reduction in risk of EAC, with ORs of 0.56 (95% CI, 0.43–0.73; $P_{trend} < .001$) and 0.63 (95% CI, 0.45–0.90; $P_{trend} = .04$), respectively. **CONCLUSIONS: Although reverse causation could, in part, explain the inverse association observed between NSAID use and EAC risk, our pooled analysis suggests a possible role for NSAIDs in prevention of adenocarcinomas of the esophagus and esophagogastric junction.**

Keywords: BEACON; Esophageal Neoplasm; Stomach Cancer; Anti-Inflammatory Agent.

The incidence of esophageal adenocarcinoma (EAC) has increased considerably in many Western countries over the past 3 decades.[1,2] The disease continues to have a very low survival rate.[3] Esophagogastric junctional adenocarcinomas (EGJAs) are a heterogeneous group of adenocarcinomas that reside within the gastric cardia and/or the gastroesophageal junction. Similar to EAC, upward trends of EGJA have been reported in Western countries in recent years.[4,5]

Inflammation, caused by factors such as gastroesophageal reflux, is believed to cause EGJA and EAC, suggesting a plausible preventative role for anti-inflammatory agents. A primary preventive mechanism for nonsteroidal anti-inflammatory drugs (NSAIDs) is believed to be the inhibition of cyclooxygenase (COX)-2 production, an enzyme that is an important mediator of inflammation.[6,7] Elevated COX-2 expression has been observed in Barrett's esophagus, a precursor lesion of EAC, with expression

Abbreviations used in this paper: BEACON, Barrett's Esophagus and Esophageal Adenocarcinoma Consortium; BMI, body mass index; CI, confidence interval; COX, cyclooxygenase; EAC, esophageal adenocarcinoma; EGJA, esophagogastric junctional adenocarcinoma; NIH, National Institutes of Health; OR, odds ratio.

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levels noted to increase with disease progression to EAC.[8,9] Experimental studies have also shown that treatment with COX-2 inhibitors can inhibit the growth in vitro of Barrett's esophagus cells, an effect potentially mediated by suppression of basic fibroblast growth factor.[10–12] Higher levels of COX-2 expression also have been detected in gastric carcinomas.[13] Although several studies have observed that COX-2 inhibitors slow the growth of gastric tumor cells and induce apoptosis, they have also suggested that this may be mediated through pathways other than suppressing COX-2.[14,15]

Frequent use of NSAIDs has been associated with a reduced risk of gastrointestinal cancers in many epidemiologic studies.[16,17] Studies conducted thus far on NSAID use have focused mainly on colorectal cancer, with a smaller but growing number of studies investigating NSAID use in relation to esophageal and gastric cancers. The majority of these studies support an inverse association between NSAID use and risk of EAC and EGJA.[18–26] Previous reviews have largely limited their evaluations of NSAID use and risk of EAC and EGJA to assessments of ever use.[27–31] It is not known whether specific characteristics of NSAID use, such as frequency or duration of use, are important in reducing the risks of specific subtypes of these cancers.

The Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) was established in 2005 in part to assemble a large sample size of well-characterized patients with EAC or Barrett's esophagus and representative controls, which would allow us to better define risk factors of Barrett's esophagus and adenocarcinomas of the esophagus and gastroesophageal junction.[32] We performed a pooled analysis of studies within the BEACON consortium, after harmonization of variables using individual-level data, to comprehensively evaluate the association between aspirin and NSAID use and the risk of EAC and EGJA.

Subjects and Methods

Study Populations

Among the 12 BEACON studies, we identified 6 with sufficient information on aspirin and nonaspirin NSAID use to contribute to the pooled analyses of EAC (Table 1). Five studies were population-based case-control studies (the Australian Study of Esophageal Cancer,[33] the Nova Scotia Barrett Esophagus Study,[34] the US Multicenter Study,[24] the Factors Influencing the Barrett's Adenocarcinoma Relationship Study,[20] and the Los Angeles County Multi-ethnic Study[35]) and one was a cohort study (the National Institutes of Health [NIH]-AARP Diet and Health Study[29]). The NIH-AARP cohort study provided data on all eligible cases and a random subset of controls (4:1) from among cohort members with follow-up through 2003. Data acquired and data pooling for each study were approved by the institutional review board or research ethics committee of the institute sponsoring the study.

Because cancers that arise from the cardia of the stomach and the gastroesophageal junction present distinct features in comparison with cancers from the distal portion of the stomach, we have chosen to define adenocarcinomas of the gastric cardia and gastroesophageal junction as EGJA in this analysis. Our analysis was restricted to white subjects because there were few nonwhite

Table 1. Description of Studies in BEACON Consortium and Selected Characteristics

Study	Years of cancer diagnosis	Country	Controls	No. of EAC cases	No. of EGJA cases	Mean age, *y* (range)[a]	Sex (% male)[a]	NSAID use (ever)			
								Controls (%)	EAC cases (%)	EGJA cases (%)	
Case-control studies											
Los Angeles County Multi-ethnic Study	1992–1997	United States	841	171	210	61.2 (22–81)	80.9	36.6	30.2	41.2	
US Multicenter Study	1993–1995	United States	624	278	246	64.6 (30–80)	79.2	41.5	31.9	38.8	
Nova Scotia Barrett Esophagus Study	2001–2003	Canada	99	56	0	55.2 (17–88)	65.7	68.4	64.8	—	
Australian Study of Esophageal Cancer	2001–2005	Australia	1512	359	419	62.0 (19–81)	71.8	78.9	76.3	75.9	
Factors Influencing the Barrett's/Adenocarcinoma Relationship Study	2002–2004	Northern Ireland	260	131	92	62.8 (24–86)	83.7	36.2	28.5	34.8	
Cohort studies											
NIH-AARP Diet and Health Study	1995–2003	United States	1978	231	173	62.9 (50–71)	64.6	87.1	87.3	85.7	
Overall			5314	1226	1140	62.3 (17–88)	73.3	68.6	56.6	59.6	

[a]Percentages represent cases and controls combined.

case subjects (n = 75, EAC; n = 96, EGJA) among the studies with available information on NSAIDs. The 6 studies contributed data on a total of 1226 EAC cases, 1140 EGJA cases, and 5314 controls.

Exposure Variables

For this analysis, the main exposures of interest were the use of aspirin, nonaspirin NSAIDs, and all NSAIDs (aspirin and nonaspirin NSAIDs combined). The questionnaires from each study were reviewed, and all questions that assessed the use of individual NSAIDs—aspirin and other nonaspirin NSAIDs—and overall NSAIDs were extracted. Questions from each study were asked in various formats (both open-ended and predefined responses) and ranged from a simple yes/no question to more detailed questions regarding the frequency and duration of use of specific drugs (Appendix 1). Data were then formatted to create a uniform exposure suitable for pooling and estimating effects of each exposure. Category cut points for both frequency and duration were chosen based on the literature and after evaluating how each study categorized these variables in their original data. Each exposure was evaluated and categorized as follows: ever (subdivided into current and former, when possible) versus nonuse, frequency of use (nonuse, 0.1 to <1/wk, ≥1 to <7/wk, ≥7/wk), and duration of use (nonuse, 0.1 to <5 years, ≥5 to <10 years, ≥10 years). Participants categorized as having nonuse were those who indicated "no" or "never" to any questions regarding their NSAID use (Appendix 1). Current use was defined as individuals who continued to take the drugs as of the interview date or indicated that the age or calendar year that they stopped taking the drugs was within 1 year of the interview date. If the number of cases in a category was too small in the pooled data set, the category was collapsed together with a neighboring category. Overall NSAID frequency and duration were calculated by combining information from both aspirin and nonaspirin NSAID use when available. If the questionnaire did not differentiate between the 2 types of NSAIDs and only asked questions on overall NSAID use, these values were then used for estimates of overall NSAID frequency and duration. For duration of overall NSAID use, we summed years of aspirin use and nonaspirin NSAID use. For frequency of overall NSAID use, we calculated a combined frequency that was weighted by the duration of aspirin use and nonaspirin NSAID use ($NSAID_{freq}$ = [($Asprin_{freq}$ × $Asprin_{duration}$) + (Nonaspirin $NSAID_{freq}$ × Nonaspirin $NSAID_{duration}$)] / [$Aspirin_{duration}$ + Nonaspirin $NSAID_{duration}$]). If information on frequency was recorded in categories, we assigned the median of each previously defined category as the value for that specific category. Actual amount or dosage for NSAID use was not available from any of the study questionnaires.

A major advantage of having access to the individual patient data from each study is that similar study-specific analytic models can be built, thus increasing the validity of their combination using a meta-analytic model. Additional variables that were acquired from each study and considered as covariates for this analysis included age, sex, body mass index (BMI), gastroesophageal reflux status (ever vs no), education, smoking exposure (pack-years), alcohol intake (drinks per day), and study center. Age was defined as age at diagnosis for cases, age at interview for controls from case-control studies, and age at baseline for participants from cohort studies. BMI was calculated by dividing weight (kg) by the square of height (m). Gastroesophageal reflux status was missing in 2 studies.[29,34] A study-specific education variable was used in analyses because a different method of categorization was used in each study. Smoking exposure was characterized by pack-years of tobacco exposure (number of cigarettes smoked per day × number of years smoked/20) and has been previously described.[32] Alcohol intake was measured as the average frequency of alcohol consumption.[36]

Statistical Analysis

The analyses were conducted in 2 stages. We first used unconditional logistic regression to calculate study-specific estimates of odds ratios (ORs) and 95% confidence intervals (95% CIs), adjusted for age (categorical: <50, 50–59, 60–69, ≥70 years), sex, BMI (categorical: <25, 25–29.9, ≥30 kg/m^2), gastroesophageal reflux (ever vs no, where available), education (study specific), smoking exposure (categorical: 0, <15, 15–29, 30–44, ≥45 pack-years), alcohol intake (categorical: 0, 1–1.9, 2–2.9, ≥3 drinks per day), and study center (applicable for multicenter studies only). Additional adjustment for antacid use (yes vs no) had minimal effect on the study-specific and pooled summary estimates, so it was not included in the final model. In all analyses of aspirin and nonaspirin NSAID use, mutual adjustment for any use of the other type of NSAID was included in each respective model. This allowed us to observe an effect that accounts for any contribution from the other type of NSAID. Tests for trends were calculated by modeling exposures as ordinal variables in multivariate models. In the second stage, we performed a pooled analysis combining study-specific ORs using a random-effects meta-analytic model to calculate a summary OR. Each summary OR represents data from only the specific studies that contributed to that exposure category; thus, a study would be excluded from an analysis if it did not generate a stable OR.

Evaluation of Heterogeneity and Effect Modification

The amount of total variation among studies due to heterogeneity was assessed using the I^2 statistic.[37] Larger I^2 values could reflect greater heterogeneity between the study-specific estimates beyond what is attributable to chance. We evaluated for potential sources of heterogeneity using stratified analyses by levels of exposure, gastroesophageal reflux symptoms, method of evaluating exposure (ie, type of question), and levels of potential confounders. To evaluate whether other variables modified the effect of NSAID use on cancer risk, we conducted analyses stratified by BMI (<25 kg/m^2, ≥25 kg/m^2), smoking status (never vs ever), sex, gastroesophageal reflux, age (<60 years, ≥60 years), and education (high school or less, more than high school). All analyses were performed using Stata software version 10.0 (StataCorp LP, College Station, TX).

Results

The included studies are described in Table 1. The mean age of EAC cases, EGJA cases, and controls was 63.7, 63.1, and 61.7 years, respectively. A large majority of cases (EAC, 88.4%; EGJA, 85.8%) and controls (68.1%) were male. The overall prevalence of ever NSAID use among controls was 69%, which varied between studies from 37% to 87%. Overall, the proportion of persons reporting ever using NSAIDs was 56.6% among EAC cases and 59.6% among EGJA cases compared with 68.6% among controls.

Overall NSAID Use

Compared with nonuse, ever use of any NSAID was statistically significantly associated with a reduced risk of EAC (OR, 0.68; 95% CI, 0.56–0.83; Table 2 and Supplementary Figure 1. Ever use of NSAIDs was inversely, but not statistically significantly, associated with risk of EGJA. Furthermore, these associations appeared to be restricted to current users of NSAIDs. Decreasing risk of EAC was observed with increasing frequency of overall NSAID use (Supplementary Figure 2). Occasional use of NSAIDs was associated with an OR of 0.66 (95% CI, 0.44–1.00) and daily or greater use was associated with an OR of 0.56 (95% CI, 0.43–0.73; $P_{trend} < .001$). NSAID use for any duration also appeared to be associated with a reduced risk of EAC, but a trend of decreasing risk with increased duration was not seen. We found no evidence of a relationship between increased frequency or duration of NSAID use and risk of EGJA.

Aspirin Use

Five studies collected information on aspirin use. Ever use of aspirin was associated with a statistically significant 23% decreased risk of EAC (95% CI, 3%–40%) and a 16% decreased risk of EGJA (95% CI, 0–29%) compared with nonuse (Table 3). The inverse association with aspirin use and risk of both outcomes appeared to be limited to current use. We observed a suggestive trend of decreasing risk of EAC associated with increasing frequency of aspirin use ($P_{trend} = .03$; Supplementary Figure 3), but there was no apparent trend with increasing duration of aspirin use ($P_{trend} = .57$). Increased frequency or duration of aspirin use was not statistically significantly associated with risk of EGJA.

Nonaspirin NSAID Use

Use of nonaspirin NSAIDs was collected in 5 BEACON studies. Overall, ever use of nonaspirin NSAIDs appeared to be statistically significantly associated with a similar reduced risk of both outcomes compared with nonuse (EAC: OR, 0.81 [95% CI = 0.67–0.96]; EGJA: OR, 0.78 [95% CI, 0.66–0.93]; Table 4). Although not statistically significant and based on a small number of cases, this association may be restricted to current users (Table 4). Beyond any use of nonaspirin NSAIDs, we did not observe a clear trend with increasing frequency or duration of nonaspirin NSAID use with risk of EAC or EGJA (Supplementary Figure 4).

Type of NSAID Use

Among controls who reported using any type of NSAID, 38% reported use of aspirin only, 22% reported use of nonaspirin NSAIDs only, and 41% reported use of both types of NSAIDs. Compared with those who reported no NSAID use, the use of either aspirin only or nonaspirin NSAIDs only appeared to be associated with almost identical reduced risks of EAC (ORs of 0.69 and 0.66) and EGJA (ORs of 0.91 and 0.91), respectively (Table 5). Individuals who reported use of both types of NSAIDs were not at significantly reduced risk of EAC; however, they had a statistically significant reduced risk of EGJA compared with those who reported individual use of aspirin or nonaspirin NSAIDs.

We further evaluated the association between ever use of aspirin and other NSAIDs and risk of each outcome through stratified analyses by other variables: BMI, smoking status, sex, gastroesophageal reflux, age, education, and NSAID question type. Risk estimates appeared similar across strata of these potential risk factors (data not shown).

Discussion

We found that users of NSAIDs, in particular those reporting current use, experienced a statistically significant lower risk of EAC than those who did not use these medications. We also observed statistically significant inverse associations between greater frequency and duration of NSAID use and risk of EAC. When the analysis was examined by type of NSAID, the magnitude of the effect for ever use of aspirin was similar to the effect for ever use of nonaspirin NSAIDs. However, there was little evidence of a dose-response effect when examining type of NSAID by increasing frequency or duration. The patterns and overall inverse association between NSAID and aspirin use and risk of EGJA appear to be similar to EAC but less striking.

An inverse relationship between NSAID use and esophageal and gastric adenocarcinomas has been reported previously in reviews and meta-analyses.[27–31] An important advantage of our pooled study is that we were able to create more standardized categories of exposure using individual-level data from each study and harmonized analytic models with respect to covariates for adjustment of potential confounding; these steps permit more comparable data than is possible using only results from published ORs, which use different sets of covariates between studies. We also built on past reviews by evaluating additional aspects of NSAID use, such as frequency, duration, and temporal factors, in a larger number of cases and controls than previous reports. In the most recently published meta-analysis, Abnet et al reported that any aspirin use was inversely associated with EAC and EGJA cancers with summary ORs of 0.64 (95% CI, 0.52–0.79) and 0.82 (95% CI, 0.65–1.04), respectively.[29] Both are similar to the estimates we observed from our pooled study. We consistently observed that the effect of aspirin and NSAID use was slightly weaker for EGJA than EAC. Although only a few reviews evaluated both EAC and EGJA,[29,30] the summary estimates reported are consistent with our observations of a stronger association with EAC. This is also consistent with past meta-analyses that reported a statistically significant reduced risk of gastric noncardia cancer with NSAID use but a weaker effect for EGJA.[28,31] Since these meta-analyses were published, one additional prospective study found an inverse association between regular use of aspirin and risk of EGJA.[26] Four additional studies conducted among high-risk cohorts of

Table 2. Association Between Aspirin and Nonaspirin NSAID Use and Risk of EAC and EGJA

	EAC				EGJA			
Exposure	No. of studies[a]	No. of cases/controls	OR (95% CI)[b]	I^2 (%)	No. of studies[a]	No. of cases/controls	OR (95% CI)[b]	I^2 (%)
Any use of NSAID								
Nonuse		462/1520	1.00			402/1490	1.00	
Ever	5	627/3408	0.68 (0.56–0.83)	17	5	617/3346	0.83 (0.66–1.03)	37
Former	3	35/56	0.94 (0.54–1.62)	0	2	25/48	1.09 (0.60–1.99)	0
Current	3	94/302	0.40 (0.24–0.67)	44	2	73/248	0.57 (0.39–0.83)	4
Frequency of NSAID use								
Nonuse		357/979	1.00			284/949	1.00	
Occasionally to less than daily	4	41/173	0.66 (0.44–1.00)	5	3	34/152	0.76 (0.48–1.21)	11
Daily or more	4	131/473	0.56 (0.43–0.73)	0	3	141/432	0.88 (0.61–1.26)	46
P_{trend}[c]			<.001				0.42	
P_{trend} (excluding nonusers)[c]			0.55				0.33	
Duration of NSAID use								
Nonuse		357/979	1.00			284/949	1.00	
<5 y	4	71/308	0.50 (0.28–0.91)	65	3	87/283	0.84 (0.50–1.40)	62
5 to <10 y	4	44/131	0.73 (0.47–1.12)	0	3	46/115	1.07 (0.57–1.99)	50
10 y or more	4	60/209	0.63 (0.45–0.90)	0	3	46/191	0.74 (0.51–1.07)	0
P_{trend}[c]			0.04				0.34	
P_{trend} (excluding nonusers)[c]			0.47				0.42	

[a]Number of studies included in a specific analysis varies based on the number of studies with contributing data (eg, studies with no participants that category or not enough cases or controls in that category to provide a study-specific estimate would not be included in the random effects meta-analysis model).
[b]Adjusted for age, sex, BMI (kg/m^2), gastroesophageal reflux, education, smoking intensity (pack-years), alcohol intake (drinks per day), and study center (when applicable).
[c]Trend tests used the category of intake as an ordinal variable (eg 0–3) and were calculated from meta-analytic pooling of study-specific ORs estimated from logistic regression models.

Table 3. Association Between Aspirin Use and Risk of EAC and EGJA

	EAC						EGJA					
Exposure	No. of studies[a]	No. of cases	No. of controls	OR[b]	(95% CI)	I^2 (%)	No. of studies[a]	No. of cases	No. of controls	OR[b]	(95% CI)	I^2 (%)
Any use of aspirin												
Nonuse		568	2207	1.00				548	2207	1.00		
Ever	5	458	2610	0.77	(0.60–0.97)	47	5	469	2610	0.84	(0.71–1.00)	16
Former	2	25	39	1.09	(0.60–1.97)	0	2	18	39	0.87	(0.45–1.67)	0
Current	2	54	200	0.42	(0.26–0.66)	22	2	58	200	0.57	(0.38–0.83)	0
Frequency of aspirin use												
Nonuse		568	2207	1.00				548	2207	1.00		
Less than weekly	2	182	1139	0.87	(0.56–1.35)	66	2	183	1139	0.78	(0.62–0.99)	0
Weekly to less than daily	5	106	639	0.77	(0.59–0.99)	0	5	115	639	0.83	(0.62–1.12)	17
Daily or more	4	164	824	0.75	(0.52–1.10)	59	4	167	824	0.87	(0.65–1.15)	31
P_{trend}[c]					0.03						0.20	
P_{trend} (excluding nonusers)[c]					0.87						0.27	
Duration of aspirin use												
Nonuse		362	1074	1.00				325	1074	1.00		
<5 y	3	40	209	0.49	(0.22–1.12)	75	3	64	209	0.79	(0.46–1.37)	59
5 to <10 y	3	31	103	0.75	(0.47–1.19)	0	3	38	103	0.96	(0.48–1.93)	55
10 y or more	3	49	151	0.85	(0.58–1.26)	0	3	36	151	0.75	(0.49–1.13)	0
P_{trend}[c]					0.57						0.44	
P_{trend} (excluding nonusers)[c]					0.35						0.38	

[a]Number of studies included in a specific analysis varies based on the number of studies with contributing data (eg, studies with no participants in that category or not enough cases or controls in that category to provide a study-specific estimate would not be included in the random effects meta-analysis model).
[b]Adjusted for any use of nonaspirin NSAID, age, sex, BMI (kg/m^2), gastroesophageal reflux, education, smoking intensity (pack-years), alcohol intake (drinks per day), and study center (when applicable).
[c]Trend tests used the category of intake as an ordinal variable (eg, 0–3) and were calculated from meta-analytic pooling of study-specific ORs estimated from logistic regression models.

Table 4. Association Between Nonaspirin NSAID Use and Risk of EAC and EGJA

	EAC						EGJA					
Exposure	No. of studies[a]	No. of cases	No. of controls	OR[b]	(95% CI)	I^2 (%)	No. of studies[a]	No. of cases	No. of controls	OR[b]	(95% CI)	I^2 (%)
Any use of nonaspirin NSAID												
Nonuse		688	2745	1.00				679	2745	1.00		
Ever	5	338	2072	0.81	(0.67–0.96)	4	5	338	2072	0.78	(0.66–0.93)	0
Former	2	20	31	1.81	(0.88–3.69)	0	2	10	31	1.30	(0.53–3.23)	0
Current	2	19	62	0.63	(0.34–1.15)	0	2	19	62	0.81	(0.45–1.47)	0
Frequency of nonaspirin NSAID use												
Nonuse		688	2745	1.00				679	2745	1.00		
Less than weekly	2	178	1156	0.80	(0.64–1.01)	0	2	188	1156	0.80	(0.64–1.00)	0
Weekly to less than daily	5	91	497	0.87	(0.66–1.14)	0	5	75	497	0.68	(0.51–0.91)	0
Daily or more	5	67	414	0.74	(0.47–1.18)	54	5	73	414	0.83	(0.62–1.10)	0
P_{trend}[c]					0.05						0.01	
P_{trend} (excluding nonusers)[c]					0.92						0.70	
Duration of nonaspirin NSAID use												
Nonuse		425	1307	1.00				404	1307	1.00		
<5 y	3	35	159	0.73	(0.44–1.22)	26	3	38	159	0.84	(0.56–1.25)	0
5 to <10 y	2	8	35	0.81	(0.19–3.41)	58	2	13	35	1.21	(0.50–2.96)	36
10 y or more	3	9	34	0.72	(0.31–1.64)	0	3	7	34	0.64	(0.26–1.55)	0
P_{trend}[c]					0.48						0.47	
P_{trend} (excluding nonusers)[c]					0.32						0.93	

[a]Number of studies included in a specific analysis varies based on the number of studies with contributing data (eg, studies with no participants in that category or not enough cases or controls in that category to provide a study-specific estimate would not be included in the random effects meta-analysis model).
[b]Adjusted for any use of aspirin, age, sex, BMI (kg/m^2), gastroesophageal reflux, education, smoking intensity (pack-years), alcohol intake (drinks per day), and study center (when applicable).
[c]Trend tests used the category of intake as an ordinal variable (eg, 0–3) and were calculated from meta-analytic pooling of study-specific ORs estimated from logistic regression models.

Table 5. Association Between Type of NSAID Use and Risk of EAC and EGJA

Exposure	EAC						EGJA					
	No. of studies[a]	No. of cases	No. of controls	OR[b]	(95% CI)	I^2 (%)	No. of studies[a]	No. of cases	No. of controls	OR[b]	(95% CI)	I^2 (%)
None		443	1490	1.00				402	1490	1.00		
Aspirin only	5	245	1255	0.69	(0.47–1.00)	69	5	277	1255	0.91	(0.71–1.17)	36
Nonaspirin NSAID only	5	125	717	0.66	(0.47–0.93)	25	5	146	717	0.91	(0.71–1.17)	0
Both	5	213	1355	0.76	(0.50–1.16)	55	5	192	1355	0.64	(0.50–0.82)	0

[a]Number of studies included in a specific analysis varies based on the number of studies with contributing data (eg, studies with no participants in that category or not enough cases or controls in that category to provide a study-specific estimate would not be included in the random-effects meta-analysis model).
[b]Adjusted for age, sex, BMI (kg/m^2), gastroesophageal reflux, education, smoking intensity (pack-years), alcohol intake (drinks per day), and study center (when applicable).

patients with Barrett's esophagus, 2 prospective and 2 retrospective, have also observed evidence of a reduced risk of progression to EAC with NSAID use.[19,38–40] A pooled analysis of 3 randomized trials of daily aspirin use and at least 5 years of treatment found a delayed but significant reduction in deaths due to EAC and EGJA after 5+ and 10+ years of post-trial follow-up, respectively.[41] Although a small, short-term trial of celecoxib/placebo among subjects with Barrett's esophagus found no change in the proportion of dysplastic biopsies between the treatment (200 mg/pill, 2 pills/day) and placebo group at 48 weeks,[42] almost half of these patients already had dysplasia at study entry; a much larger randomized trial, including adequate numbers of patients without dysplasia, is needed to fully explore this hypothesis. A randomized trial of aspirin and proton pump inhibitors among patients with Barrett's esophagus is currently ongoing in the United Kingdom.[43] Results from this trial will assist in the ongoing effort to further examine the relationship between aspirin and the development of EAC.

In our study, the association with ever use of aspirin and nonaspirin NSAIDs was generally similar for EAC risk. This is in agreement with findings from other reviews that evaluated the effect of NSAIDs by type. All of our analyses were mutually adjusted for the other type of NSAID, which did not change any of the observed associations substantially. This suggests that although similar in effect estimates, both aspirin and nonaspirin NSAID use appear to have an individual effect on EAC risk above and beyond use of the other type of NSAID. That is, exposure to any member of this class of medication further reduces the risk of EAC. The similar effects of aspirin and nonaspirin NSAID use are substantiated further by the nearly identical associations observed between individuals who reported using aspirin only and individuals who reported using nonaspirin NSAIDs only with EAC and EGJA risk. Because experimental studies have reported similar pathways and actions of aspirin and other NSAIDs, such as inhibiting COX-2, decreasing inflammation, increasing apoptosis, and decreasing proliferation, it seems reasonable that there would be little difference between their effects on EAC or EGJA risk.[44,45]

Frequency of NSAID use appeared to be more strongly associated with a reduction in EAC risk than duration of NSAID use in this analysis. Our analysis found an inverse relationship with increased frequency of NSAID use ($P_{trend} < .001$) but a consistent reduced risk of EAC with any level of duration. A similarly strong inverse dose response between frequent NSAID use and esophageal cancer was also reported in the meta-analysis by Corley et al.[27] None of the previous EAC meta-analyses evaluated the effect of duration of use, so we were unable to compare our results with others. Although we observed an association with risk of EAC, we found no significant associations among the highest categories of frequent or longer duration of NSAID use and risk of EGJA. In a meta-analysis by Wang et al, an inverse association with "regular" or frequent use of NSAIDs and gastric cancer was observed; however,

there was inadequate evidence to suggest an association with duration of NSAID use in their analysis.[28] The interpretation of results on frequent NSAID use from the meta-analysis by Wang et al, however, is limited due to the inclusion of a mixture of gastric cancer sites and varying definitions of "regular" NSAID use across studies included in their meta-analysis.

Although analyses were limited to a subset of studies, in our study it appears that the reduced risk of EAC and EGJA was restricted to those who reported current use of NSAIDs. Past reviews have not attempted to summarize the effect of current NSAID status on risk of either EAC or EGJA. This is most likely attributable to the lack of published estimates, whereas we were able to use raw data from 3 of the 6 BEACON studies to construct this variable. The current NSAID users in our study tended to report frequent NSAID use (median, ~1 pill/day) and a moderate duration of use (median, 5 years). A similar pattern with current NSAID status has been observed in the one prospective study of patients with Barrett's esophagus. Vaughan et al[19] observed that current NSAID use at baseline was associated with a significantly lower risk of EAC, which was stronger in a subset of patients who were deemed to be current users for the full duration of follow-up (median, 5.5 years).

Results from our study could suggest a possible short-term protective effect of NSAIDs on EAC and EGJA risk, because we observed an effect with current users and higher frequency, but not longer duration. However, because our pooled analysis consisted primarily of data from case-control studies, some of the observed effect could be due to reverse causation. Continued NSAID use can lead to erosive tissue damage in the gastrointestinal tract, which may result in patients with gastroesophageal reflux discontinuing NSAID use. However, the supplemental analyses in this study did not support this possibility; a similar effect of aspirin and NSAID use and risk of EAC and EGJA was observed among individuals with or without gastroesophageal reflux. In addition, findings from the NIH-AARP study, a prospective cohort included in this analysis, were similar to findings of EGJA risk among case-control studies in this analysis. If replicated in further prospective studies and randomized trials, this could have implications on the use of NSAIDs as a potential preventative measure.

Our pooled study has a number of strengths as well as limitations. It included and combined data from 6 population-based case-control and cohort studies. This allowed for a large sample size and suitable statistical power to evaluate overall main effect associations, although the case numbers were still small in some strata and limited our power to fully evaluate effect modification. Combining data from a subset of our studies with extensive questions on use also gave us the ability to evaluate characteristics of NSAID use, which has been limited in past reviews. There was some variability among questions from different studies; in particular, we noticed 2 general patterns in how questions were asked. When the lead-in question included the definition of "regular use," the prevalence of NSAID use among controls was approximately 40%, whereas broader questions reported a prevalence of approximately 70% among controls (Appendix 1). Despite the 2 patterns of questions, results stratified by question type showed consistently inverse associations. There were also some minor differences on how frequency of use was collected: open-ended versus predetermined responses, and what time period served as the reference period for estimating use (Appendix 1). Assuming the time period was representative of usual use, we were able to define NSAID use in the same way across studies. Detailed individual-level data on known and suspected risk factors for EAC and EGJA were available for pooling from each study, thus allowing us to control for possible confounding from a standard set of risk factors across each study. There was some evidence of moderate heterogeneity between study populations; however, overall, there appears to be little evidence of heterogeneity across the majority of results except for duration of aspirin. Overall duration of NSAID use might have been overestimated, because we were unable to take into account potential concurrent use of aspirin and nonaspirin NSAIDs in the calculation. However, we reevaluated overall NSAID duration, taking into account concurrent use in 2 studies that collected sufficient data to perform this analysis, and found that there was very little difference in study-specific estimates. Another limitation of our data is that no dosage information was collected in any of the studies. Inclusion of NSAID amounts would have provided a better indicator of drug exposure than frequency and duration alone. Because most participating studies were case-control studies, data from these studies may be subject to biases; however, data from each study were obtained rapidly after enrollment and collected with detailed procedures. Results were also generally similar to those of the cohort study. Finally, we were unable to directly evaluate whether NSAID use varied by Barrett's esophagus status and whether this would have had an effect on reported associations, because the number of cases with information on Barrett's esophagus diagnosis (n = 93) was not large enough to conduct any suitably powered analyses. However, with the small proportion of cancer cases with a prior diagnosis of Barrett's esophagus, any effect on the overall results is likely to be small.

In summary, findings from this pooled analysis support the hypothesis that NSAID use provides potential benefits in preventing esophageal and esophagogastric adenocarcinomas. There is also evidence to suggest that increased frequency and longer duration of overall NSAID use is associated with further reduced risk of EAC, but these associations are not present when evaluated by NSAID type. Results from stratified analyses indicate that aspirin and nonaspirin NSAIDs have a similar effect on EAC risk overall. Although the use of NSAIDs as a chemopreventive strategy is promising, the effectiveness of NSAIDs still has to be evaluated in randomized trials before this approach is advanced clinically.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2011.11.019.

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Conflicts of interest

The authors disclose no conflicts.

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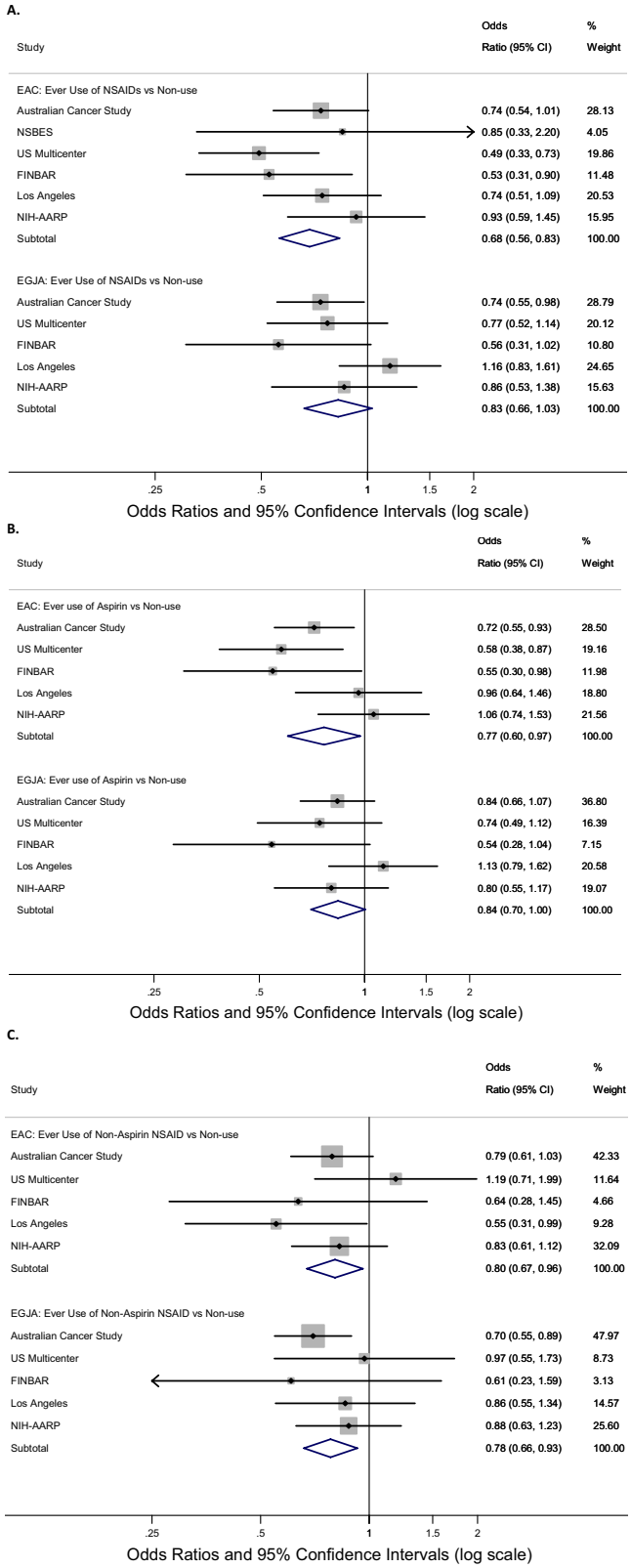
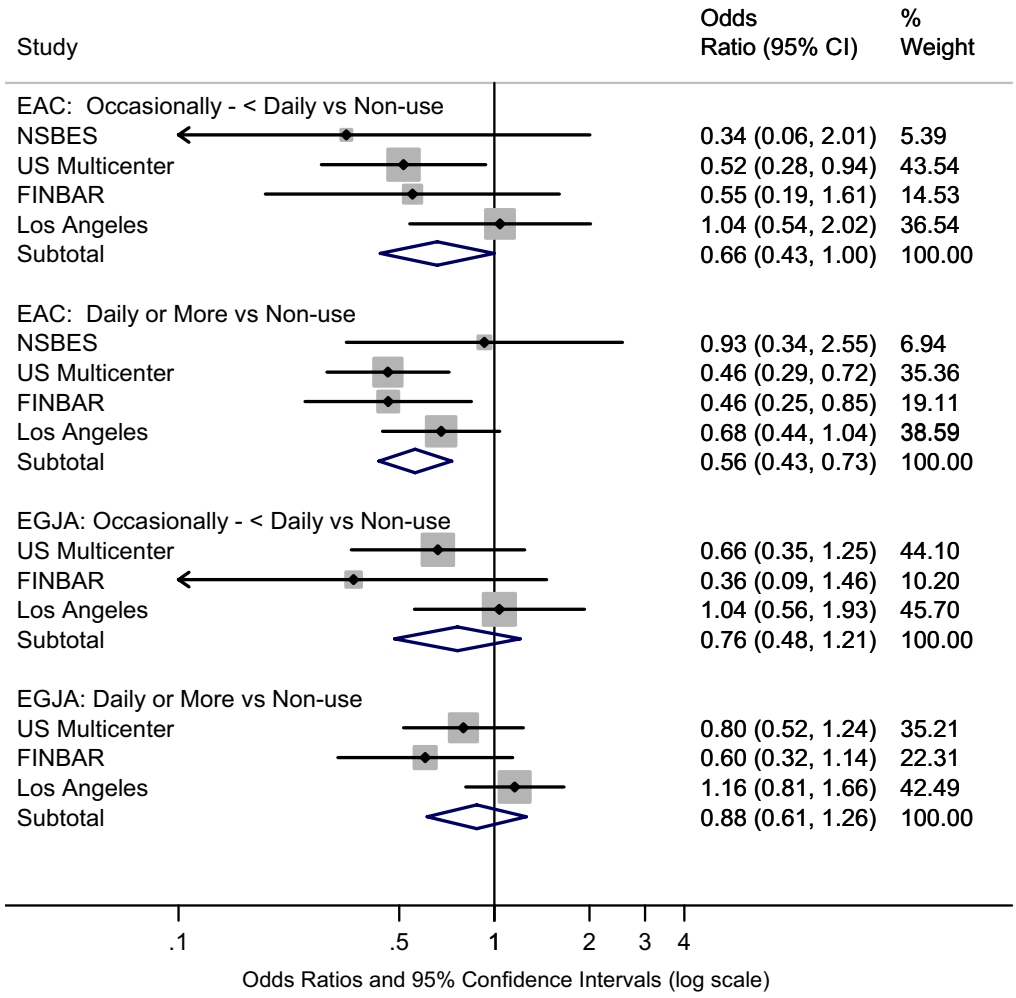
Appendix 1. Individual Study Data Used for Pooled Analysis

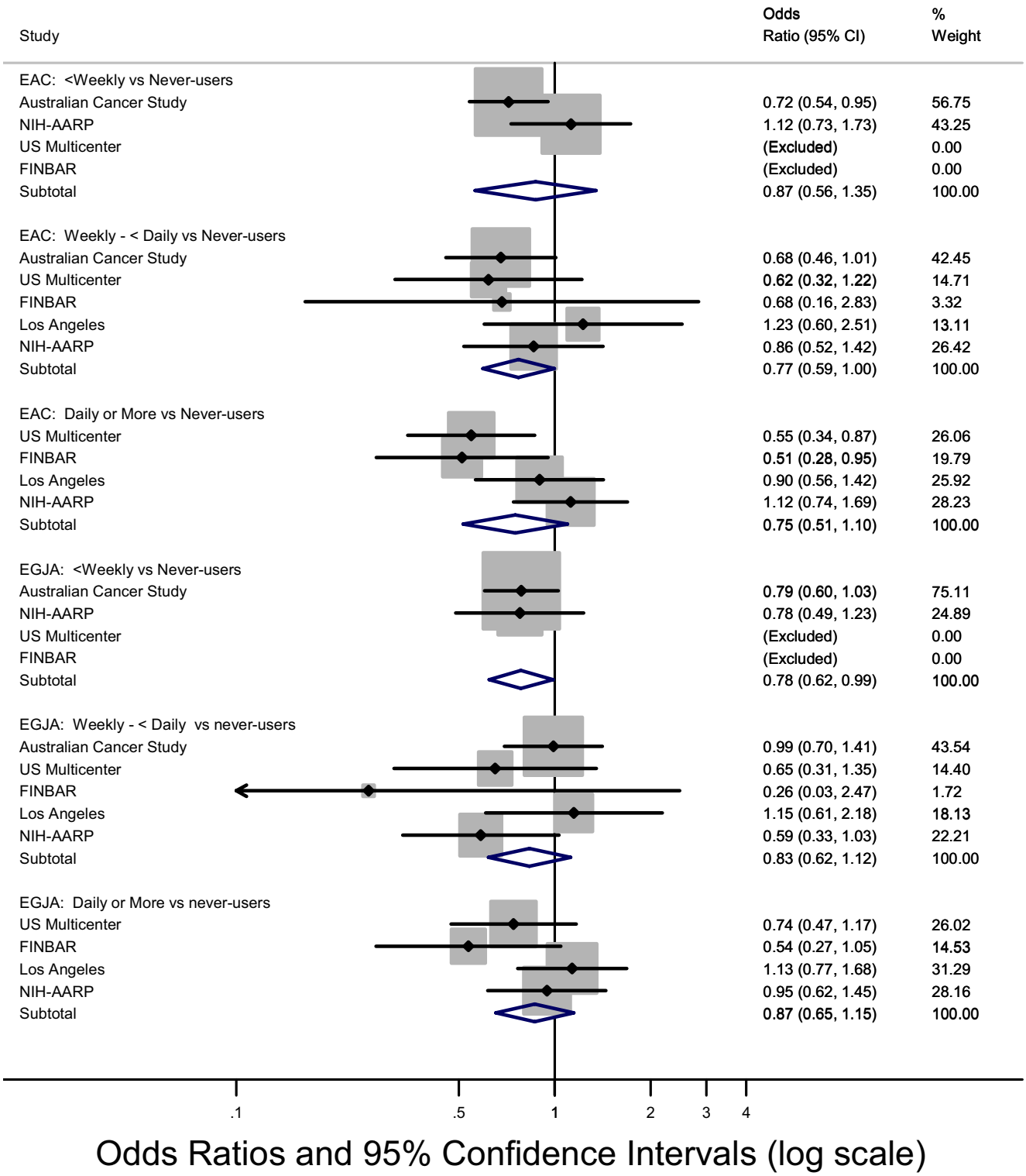
Studies included in this analysis	Questions asked	Reference period	Contributed data on frequency of use of aspirin, other NSAIDs/precoded categories or continuous	Contributed data on duration of use of aspirin, other NSAIDs/precoded categories or continuous
Los Angeles County Multi-ethnic Study	Have you ever taken medications regularly (at least 2 times per week for 1 month or more)?	2 y before diagnosis	Yes, continuous	Yes, continuous
US Multicenter Study	Before a year ago, did you take any of the medications at least 1/wk, for 6 months or longer?	1 y before diagnosis	Yes, continuous	Yes, continuous
Nova Scotia Barrett Esophagus Study	Have you ever used any of the following medications?	5 y before diagnosis	NSAIDs overall, continuous	NSAIDs overall, continuous
Australian Study of Esophageal Cancer	How often have you taken the following medications during the past 5 years?	Past 5 y at entry	Yes, categories (occasionally, <1/mo, 2–3 times/mo, 1 time/wk, 2–3 times/wk, 4–7 times/wk, 2 or more times/day)	No
Factors Influencing the Barrett's/Adenocarcinoma Relationship Study	Did you ever take any of these medications regularly (at least 1/wk for 6 mo or longer)?	1 y before diagnosis	Yes, continuous	Yes, continuous
NIH-AARP Diet and Health Study	During the past 12 months, did you take any of the following medications?	Past 1 y at entry	Yes, categories (<2 times/mo, 2–3 times/mo, 1–2 times/wk, 3–4 times/wk, 4–5 times/wk, 1 time/day, 2 or more times/day)	No



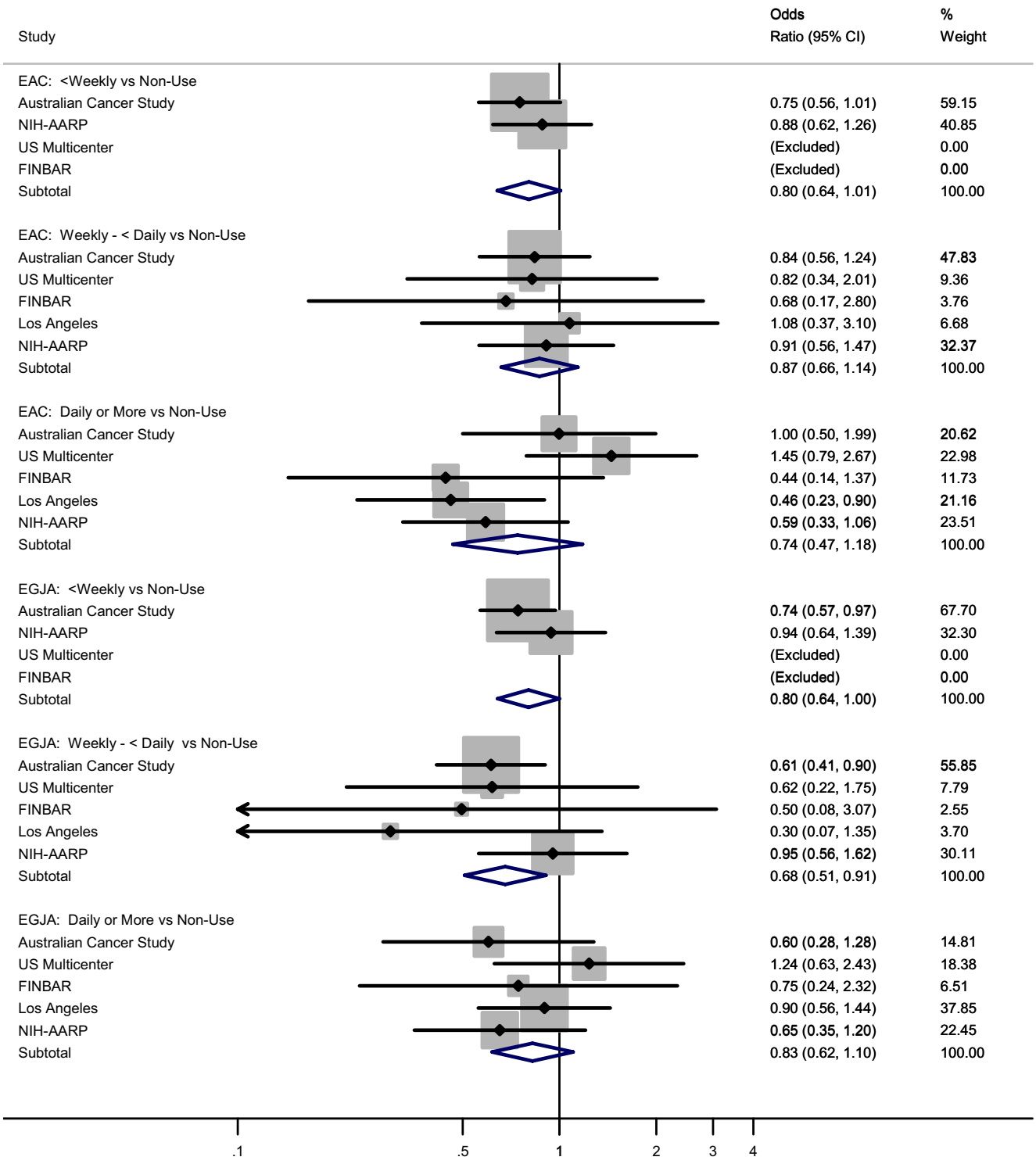
Supplementary Figure 1. Forest plot for the association of esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma and ever use of (*A*) NSAIDs (all), (*B*) Aspirin, and (*C*) Non-aspirin NSAIDs. Summary odds ratios and 95% confidence intervals were estimated using a random effects meta-analytic model. All statistical tests were two-sided. % weight describes the weighting each study contributes to the summary odds ratio. The dot on each square represents the study-specific odds ratio, and the size of the surrounding square is an illustrative representation of study weighting. The horizontal lines represent the 95% confidence intervals. The unfilled diamond represents the summary odds ratio.



Supplementary Figure 2. Forest plot for the association of esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma and frequency of overall NSAID (aspirin and non-aspirin NSAID) use. Summary odds ratios and 95% confidence intervals were estimated using a random effects meta-analytic model. All statistical tests were two-sided. % weight describes the weighting each study contributes to the summary odds ratio. The dot on each square represents the study-specific odds ratio, and the size of the surrounding square is an illustrative representation of study weighting. The horizontal lines represent the 95% confidence intervals. The unfilled diamond represents the summary odds ratio.



Supplementary Figure 3. Forest plot for the association of esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma and frequency of aspirin use. Summary odds ratios and 95% confidence intervals were estimated using a random effects meta-analytic model. All statistical tests were two-sided. % weight describes the weighting each study contributes to the summary odds ratio. The dot on each square represents the study-specific odds ratio, and the size of the surrounding square is an illustrative representation of study weighting. The horizontal lines represent the 95% confidence intervals. The unfilled diamond represents the summary odds ratio.



Supplementary Figure 4. Forest plot for the association of esophageal adenocarcinoma and esophagogastric junctional adenocarcinoma and frequency of non-aspirin NSAID use. Summary odds ratios and 95% confidence intervals were estimated using a random effects meta-analytic model. All statistical tests were two-sided. % weight describes the weighting each study contributes to the summary odds ratio. The dot on each square represents the study-specific odds ratio, and the size of the surrounding square is an illustrative representation of study weighting. The horizontal lines represent the 95% confidence intervals. The unfilled diamond represents the summary odds ratio.