Supplementary materials

Supplementary Figure S14. Forest plot of subgroup analyses of aspirin intake and gastric cancer risk for the duration of >10 years use group.
Supplementary Figure S15. Forest plot of subgroup analyses of COX-2 inhibitors intake and gastric cancer risk for the frequency of daily use group.
Supplementary Figure S16. Forest plot of subgroup analyses of COX-2 inhibitors intake and gastric cancer risk for the duration of ⩽1 year use group.
Supplementary Figure S17. Forest plot of subgroup analyses of COX-2 inhibitors intake and gastric cancer risk for the duration of 2 to 5 year use group.
Supplementary Figure S18. Forest plot of subgroup analyses of other NSAIDs intake and gastric cancer risk for the frequency of 1 to 15 times per month use group.
Supplementary Figure S19. Forest plot of subgroup analyses of other NSAIDs intake and gastric cancer risk for the frequency of 16 to 29 times per month use group.
Supplementary Figure S20. Forest plot of subgroup analyses of other NSAIDs intake and gastric cancer risk for the frequency of >30 times per month use group.

Supplementary Table S1. Search strategy.

1. Aspirin
2. Cyclooxygenase inhibitors
3. NSAIDs
4. Non-NSAIDs
5. Anti-inflammatory
6. Celecoxib
7. COX
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. Gastric
10. Stomach
11.9 OR10
12.Cancer
13.Neoplasm
14.Carcinoma
15.Adenocarcinoma
16.Turmor
17.12 OR 13 OR 14 OR 15 OR 16
18.8 AND 11 AND 17

Supplementary Table S2. Characteristics of the included studies

Author/Year	Study period	Age(years)/ sex	No. of case/control (E/N)	Exposure assessment	Drug(s)
Gillies(10)/1968	1967	(M/F)	25/25	Interview	Aspirin
Isomaki(33)/1978	1967–1973	(M/F)	46 101/46101	Database	Therapy for arthritis
Gridley(34)/1993	1965–1984	(M/F)	11683/11683	Database	Therapy for arthritis
Thun(35)/1993	1982–1988	(M/F)	635031/445058	Interview	Aspirin
Schreinemachers(36)/1994	1971–1987	25-74 (M/F)	7438/5230	Interview	Aspirin
Cibere(37)/1997	1966–1995	(M/F)	862/862	Database	Therapy for arthritis
TPT(38)/1998	1984-1989	45-69 (M)	2545/2549	Interview	Aspirin
Farrow(14)/1998	1993–1995	30-79 (M/F)	612/687	Interview	Aspirin, and non-aspirin NSAIDs
Amjad(39)/1998	1993-1996	37-69 (M/F)	4/36	Database	Aspirin, and non-aspirin NSAIDs
Zaridze(40)/1999	1996–1997	(M/F)	165/893	Interview	Aspirin, and non-aspirin NSAIDs
Suleiman(41)/2000	1990–1992	(M/F)	82/30	Database	NSAIDs
Langman(42)/2000	1993–1995	(M/F)	496/1522	Database	NSAIDs
Coogan(43)/2000	1997–1998	<70 (M/F)	3621/2462	Interview	NSAIDs
Akre(11)/2001	1989–1995	40-79 (M/F)	409/918	Interview	Aspirin
Fischbach(44)/2001	1993-1994	18-65 (M/F)	137/147	Interview	Non-aspirin NSAIDs
Sorensen(45)/2003	1989–1997	(M/F)	172057/172057	Database	Non-aspirin NSAIDs
S Friis(46)/2003	1989-1995	(M/F)	9430/20040	Database	Aspirin
Nomura(47)/2003	1993–1999	18-65 (M/F)	192/553	Interview	NSAIDs
Ratnasinghe(15)/20	1971–1980	25-74 (M/F)	14838/7996	Interview	Aspirin

04

Gammon(21)/2004	1993–1995	30-79 (M/F)	395/647	Interview	Aspirin, and NSAIDs
Cook NR(48)/2005	1992–2004	>45 (F)	19934/19942	Interview	Aspirin
Lindblad(49)/2005	1994–2001	40-84 (M/F)	8084/14264	Database	Aspirin, and non-aspirin NSAIDs
Martin W(50)/2005	1998-1999	(M/F)	184/432	Database	Aspirin, and non-aspirin NSAIDs
HB Yang(51)/2006	---	(M/F)	108/142	Database	Non-aspirin NSAIDs
Wai K(52)/2006	2001-2002	18-70 (M/F)	107/106	Interview	Non-aspirin NSAIDs
Fortuny(53)/2007	1980–2002	(M/F)	5520/3396	Database	Aspirin, and non-aspirin NSAIDs
Flossmann(12)/2007	1978-2001	(M/F)	9112/4552	Interview	Aspirin
Duan L(54)/2008	1992–1997	30-74 (M/F)	618/1456	Interview	Aspirin, and non-aspirin NSAIDs
Sadeghi(56)/2008	2001–2005	18-79 (M/F)	1197/809	Interview	Aspirin, and non-aspirin NSAIDs
Figueroa(57)/2009	1993-1995	30-79 (M/F)	488/574	Interview	Aspirin, and non-aspirin NSAIDs
Cathrine(13)/2009	1993-1995	30-79 (M/F)	138/178	Interview	Aspirin, and non-aspirin NSAIDs
Abnet CC(28)/2009	1995-2003	(M/F)	227198/83917	Interview	Aspirin, and non-aspirin NSAIDs
Epplein M(58)/2009	1993-2004	30-79 (M/F)	86695/82597	Interview	Aspirin, and non-aspirin NSAIDs
Wu(26)/2009	1998-2004	>20 (M/F)	25145/27016	Database	NSAIDs
Manas(59)/2009	2004-2006	23-91 (M/F)	113/189	Interview	NSAIDs
Steevens(60)/2010	1986-2002	55-70	262/3700	Database	NSAIDs

		(M/F)			
Yanaoka(61)/2010	2003-2005	(M/F)	26/21	Interview	NSAIDs (COX-2 inhibitor)
Gonzalez(62)/2010	1988-2007	25-69 (M/F)	225/253	Interview	NSAIDs
Bertuccio(63)/2010	1997-2007	22-80 (M/F)	67/705	Database	NSAIDs
Rothwell(27)/2011	1979-2009	(M/F)	10155/15515	Interview	Aspirin
Lee J(25)/2012	1999-2008	(M/F)	531/1435	Database	Aspirin
Wong(29)/2012	2002-2009	35-64 (M/F)	452/467	Interview	NSAIDs (COX-2 inhibitor)
Sheu(23)/2012	2010-2011	(M/F)	70/70	Interview	NSAIDs (COX-2 inhibitor)
Yanmin Wu(22)/2013	2009-2011	29-75 (M/F)	74/950	Database	NSAIDs
Gong(24)/2014	2000-2010	56-71 (M/F)	81/573	Database	Aspirin
Ajdarkosh(22)/2015	2010-2013	40-80 (M/F)	122/566	Database	Aspirin, and non-aspirin NSAIDs
Sungmo Jung(24)/2015	2007-2011	53-73 (M/F)	158/883	Interview	Aspirin

Abbreviations: E: exposure, N: non-exposure, F: female, M: male, BMI: body mass index, NSAIDs: non-steroidal anti-inflammatory drugs, COX-2: cyclo-oxygen-ase-2.

Supplementary Table S3. Methodological quality of case-control studies included in the meta-analysis

Author/Year	Selection				Comparability	Exposure			Total quality score	Good quality
	Adequate definitio	Representativeness of cases	Selection of controls	Definition of controls		Exposure ascertainment	Same method of ascertainment	Non-Response rate		

	n of cases									
Gillies(10)/1968	☆	☆	-	☆	☆	☆	☆	☆	7	Yes
Farrow(14)/1998	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Amjad(39)/1998	☆	☆	-	☆	☆☆	☆☆	☆	-	8	Yes
Zaridze(40)/1999	☆	☆	-	☆	☆☆	☆	☆	☆	8	Yes
Suleiman(41)/2000	☆	☆	☆	☆	☆	☆☆	☆	-	8	Yes
Langman(42)/2000	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Coogan(43)/2000	☆	☆	-	☆	☆☆	☆	☆	-	7	Yes
Akre(11)/2001	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Nomura(47)/2003	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Gammon(21)/2004	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Lindblad(49)/2005	☆	☆	-	☆	☆	☆	☆	-	6	No
Martin W(50)/2005	☆	☆	-	☆	☆☆	☆☆	☆	☆	9	Yes
HB Yang(51)/2006	☆	☆	-	☆	☆☆	☆☆	☆	-	8	Yes
Fortuny(53)/2007	☆	☆	☆	☆	☆☆	☆	☆	-	8	Yes
DuanL(54)/2008	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Sadeghi(56)/2008	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Figueroa(57)/2009	☆	☆	☆	☆	☆☆	☆	☆	-	8	Yes
Cathrine(13)/2009	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Bertuccio(63)/2010	☆	☆	-	-	☆☆	☆	☆	-	6	No
Lee J(25)/2012	☆	☆	-	☆	☆	☆	☆	☆	7	Yes
Yanmin Wu(22)/2013	☆	☆	-	-	☆☆	☆	☆	-	6	No
Gong(24)/2014	☆	☆	-	☆	☆☆	☆	☆	-	7	Yes
Ajdarkosh (22)/2015	☆	☆	-	☆	☆☆	☆	☆	☆	8	Yes

Supplementary Table S4. Methodological quality of cohort studies included in the meta-analysis.

Author/ Year	Selection				Comparability	Exposure			Total quality score	Good quality
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	outcome of interest was not present at start		Assessment of outcome	Was follow up long enough for the outcome to occur	Adequacy of follow up of cohorts		
Isomaki (33)/1978	☆	☆	☆	☆	☆	☆	-	☆	7	Yes
Gridley (34)/1993	☆	☆	☆	☆	-	☆	☆	☆	7	Yes
Thun(35)/1993	-	☆	☆	☆	☆☆	☆	-	☆	7	Yes
Schreinemachers(36)/1994	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Cibere(37)/1997	-	☆	☆	☆	☆	☆	☆	☆	7	Yes
Sorensen(45)/2003	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
S Friis(46)/2003	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Ratnasinghe(15)/2004	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Abnet CC(28)/2009	☆	☆	☆	☆	☆☆	☆	-	☆	8	Yes
Epplein M(58)/2009	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Yes
Manas(59)/2009	-	☆	☆	☆	☆☆	☆	-	☆	7	Yes
Wu(26)/2009	☆	☆	☆	☆	☆☆	☆	-	☆	8	Yes
Steevens(60)/2010	☆	☆	☆	☆	☆☆	☆	☆	☆	8	Yes
Gonzale	-	☆	☆	☆	☆☆	☆	☆	☆	8	Y

z(62)/2010										es
Sungmo Jung(24)/2015	-	☆	☆	☆	☆☆	☆	-	☆	7	Yes

Supplementary Table S5. Methodologicalqualityof RCTs included in the meta-analysis.

Trial	Generation of the allocation sequence	Allocation concealment	Blinding	Follow-up	Sample size calculation	Intention-to-treat analysis	Methodological quality
TPT(38)/1998	Adequate	Adequate	Adequate	Adequate	Yes	Yes	High
Fischbach(44)/2001	Adequate	Adequate	Adequate	Adequate	Yes	No	High
Cook NR(48)/2005	Adequate	Adequate	Adequate	Adequate	Yes	Yes	High
Wai K(52)/2006	Adequate	Unclear	Unclear	Adequate	Yes	Yes	Low
Flossmann(12)/2007	Adequate	Adequate	Adequate	Adequate	Yes	Yes	High
Yanaoka(61)/2010	Unclear	Unclear	Unclear	Adequate	Yes	Yes	Low
Rothwell(27)/2011	Adequate	Adequate	Adequate	Adequate	Yes	Yes	High
Wong(29)/2012	Adequate	Adequate	Adequate	Adequate	Yes	Yes	High
Sheu(23)/2012	Unclear	Unclear	Unclear	Adequate	Yes	Yes	Low

Supplementary Table S6. Dose-response analysis.

Exposure type	Dose of use			
	Dose (mg/day)	NO. of reports	RR (95%)	P
Aspirin	<200	5	0.63(0.49,0.81)	<0.0001
	200-750	2	0.76(0.59,0.98)	0.035
	>750	1	0.94(0.58,1.54)	0.816
COX-2 inhibitors	25	1	0.42(0.14,1. 29)	0.130
	200	2	0.50(0.30,0.84)	0.009
	>200	2	0.30(0.09,1.07)	0.064
Other NSAIDs	100	1	0.72(0.53,0.88)	0.037

Abbreviations: RR, relative risk, RCT: Randomized, Placebo-Controlled Trial, HCC: hospital-based case-control, PCC: population-based case-control, COX-2: cyclooxygenase-2, NSAIDs: nonsteroidal anti-inflammatory drugs.

Supplementary Table S7. Subgroup analyses of anti-inflammatory drug intake and gastric cancer risk.

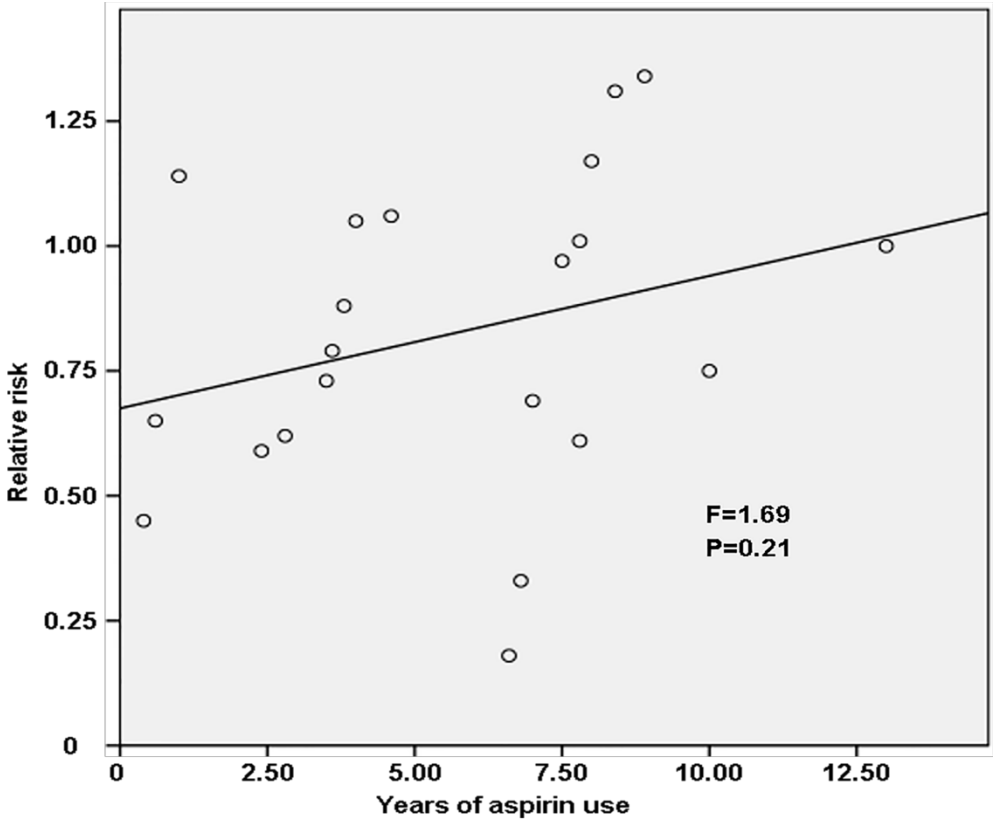
Group	NO. of reports	RR (95%)	Heterogeneity test		
			χ^2	P	I^2(%)
Total	47	0.78(0.71,0.85)	216.43	<0.0001	78.70
Geographic area					
North America	17	0.71(0.64,0.79)	44.83	<0.0001	64.30
Europe	17	0.83(0.72,0.96)	49.51	<0.0001	67.70
Asia	11	0.82(0.61,1.10)	50.76	<0.0001	80.30

Australia	2	0.87(0.61,1.25)	0.37	0.544	0.00
Site of cancer					
Cardia	13	0.80(0.73,0.87)	21.50	0.044	44.20
Non-cardia	10	0.63(0.54,0.73)	36.25	<0.0001	75.20
Study quality					
High	41	0.74(0.71,0.77)	65.56	0.007	39.00
Low	6	1.19(0.96,1.47)	11.31	0.046	55.80
Publication year					
≤2000	18	0.67(0.62,0.73)	20.04	0.066	40.10
>2000	29	0.81(0.72,0.90)	165.11	<0.0001	80.00
Sample size					
≤1000	18	0.76(0.67,0.86)	16.68	0.476	0.00
>1000	29	0.79(0.71,0.89)	197.36	<0.0001	85.8

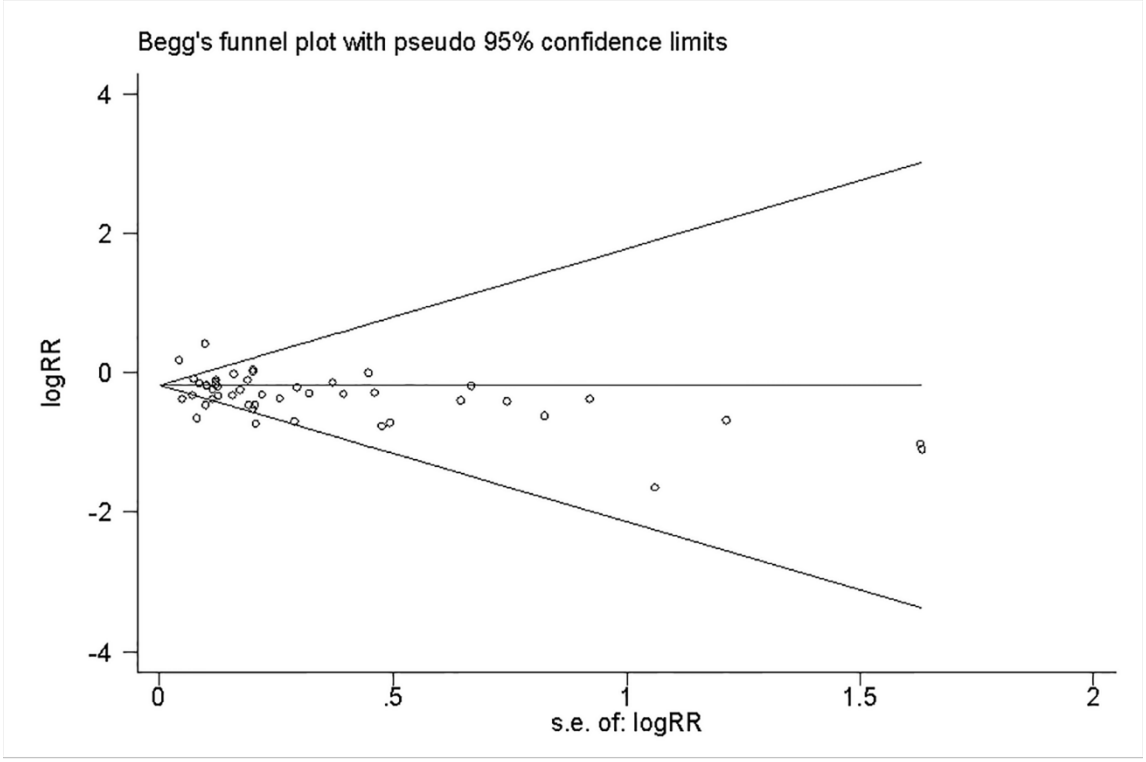
Supplementary Table S8. Meta-regression analysis.

Variable	Coefficient	Standard error	P value	95% CI
Study design	1.034	0.07	0.64	0.90 - 1.19
Geographic area	0.94	0.04	0.10	0.87 - 1.01
Study quality	0.61	0.06	<0.0001	0.51-0.75
Publication year	1.18	0.11	0.09	0.98 – 1.43
Drug type	1.03	0.06	0.60	0.92-1.16
Study size	1.09	0.12	0.45	0.45 - 1.01

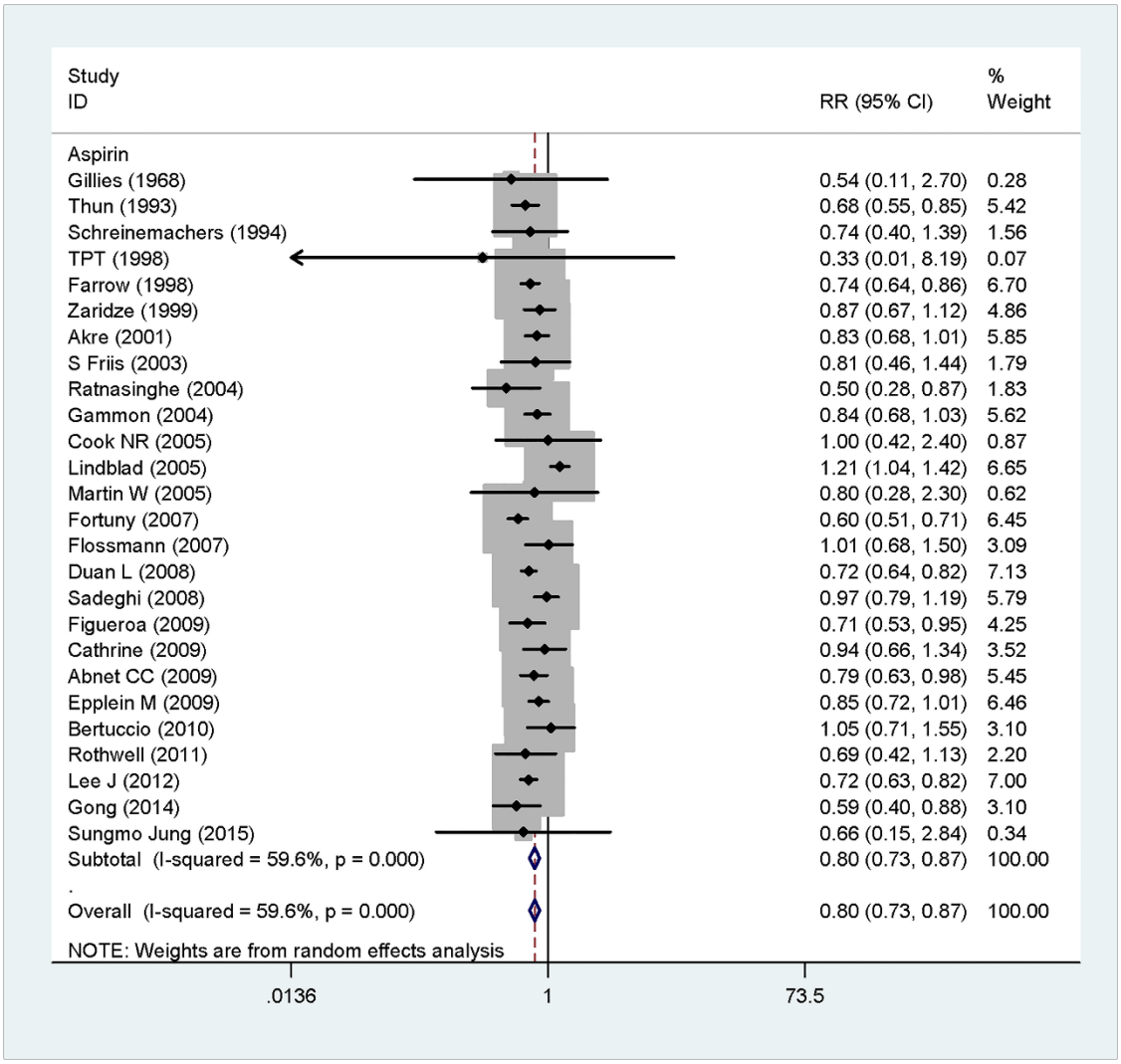
Supplementary Figure S1. Association between years of aspirin ingestion and risk of gastric cancer obtained by the linear regression model. P for linear trend= 0.210. Solid line represents the estimated relative risk (RR) and the point represent the exact RR and years of use for each included study.



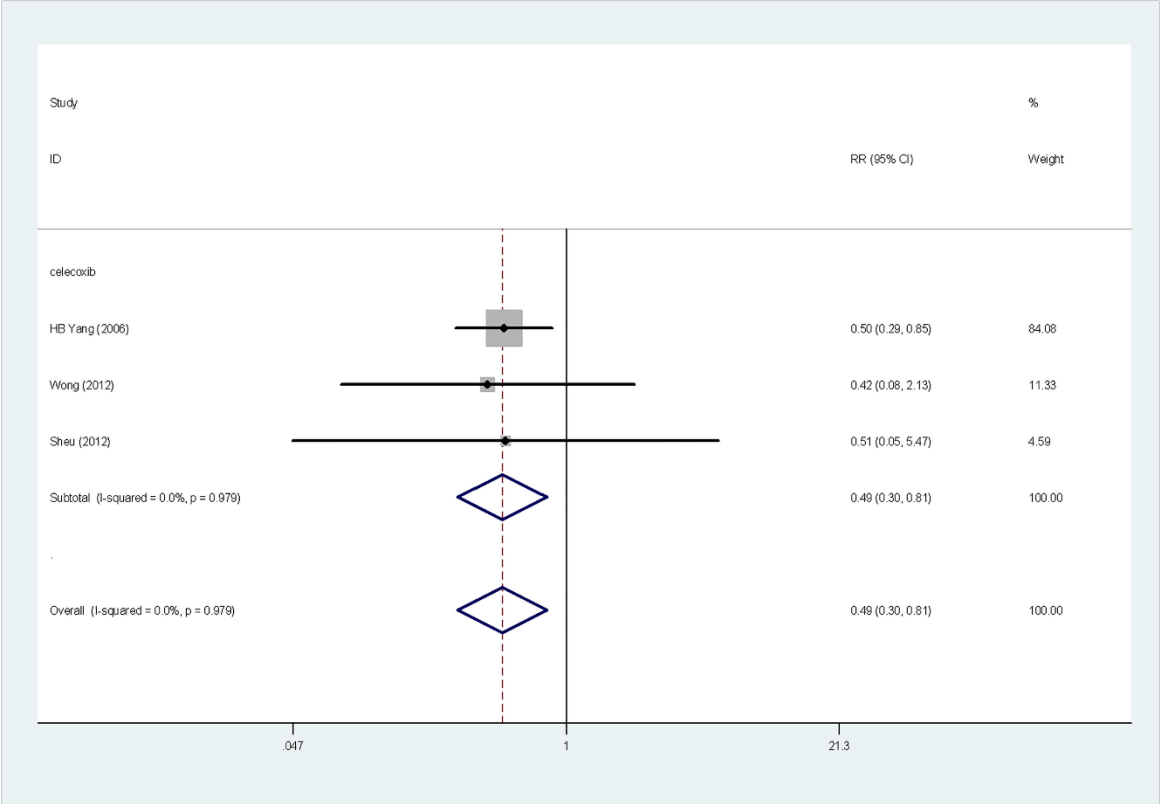
Supplementary Figure S2. Begg's funnel plot with pseudo 95% confidence limits. RR, relative risk. Each dot represents a single study for the indicated association.



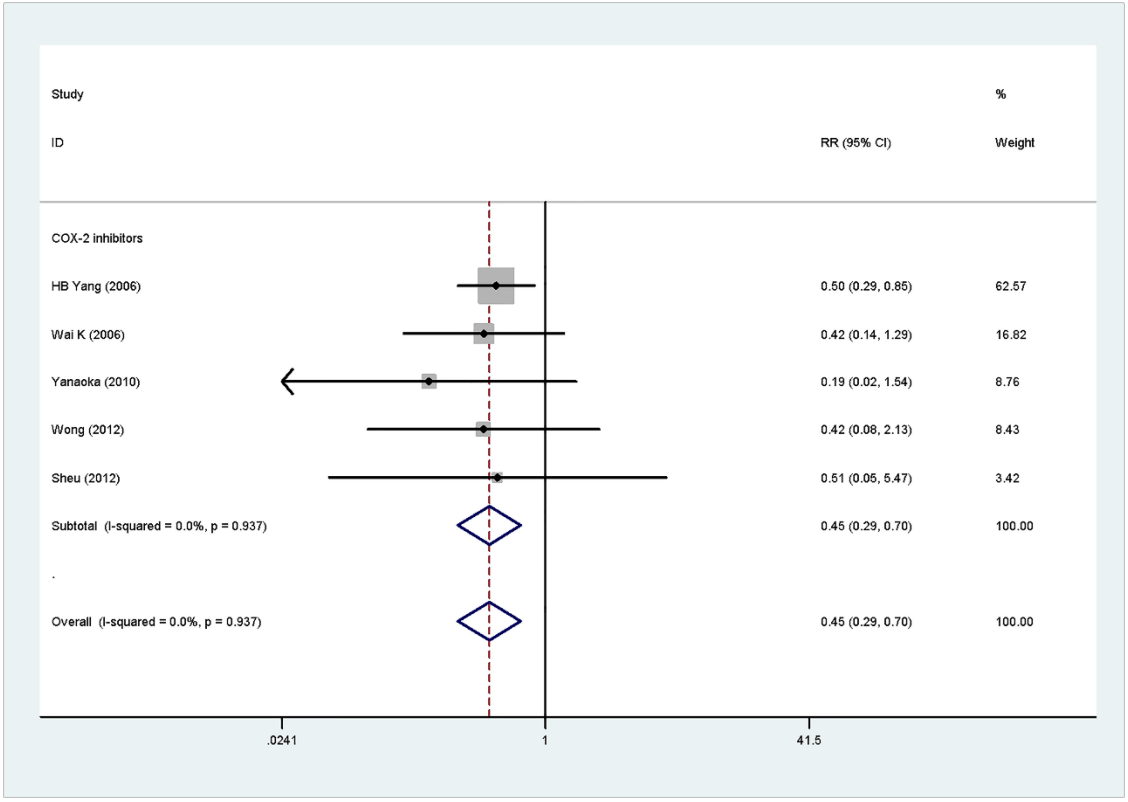
Supplementary Figure S3. Forest plot of subgroup analyses of anti-inflammatory drug intake and gastric cancer risk for aspirin group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with aspirin intake.



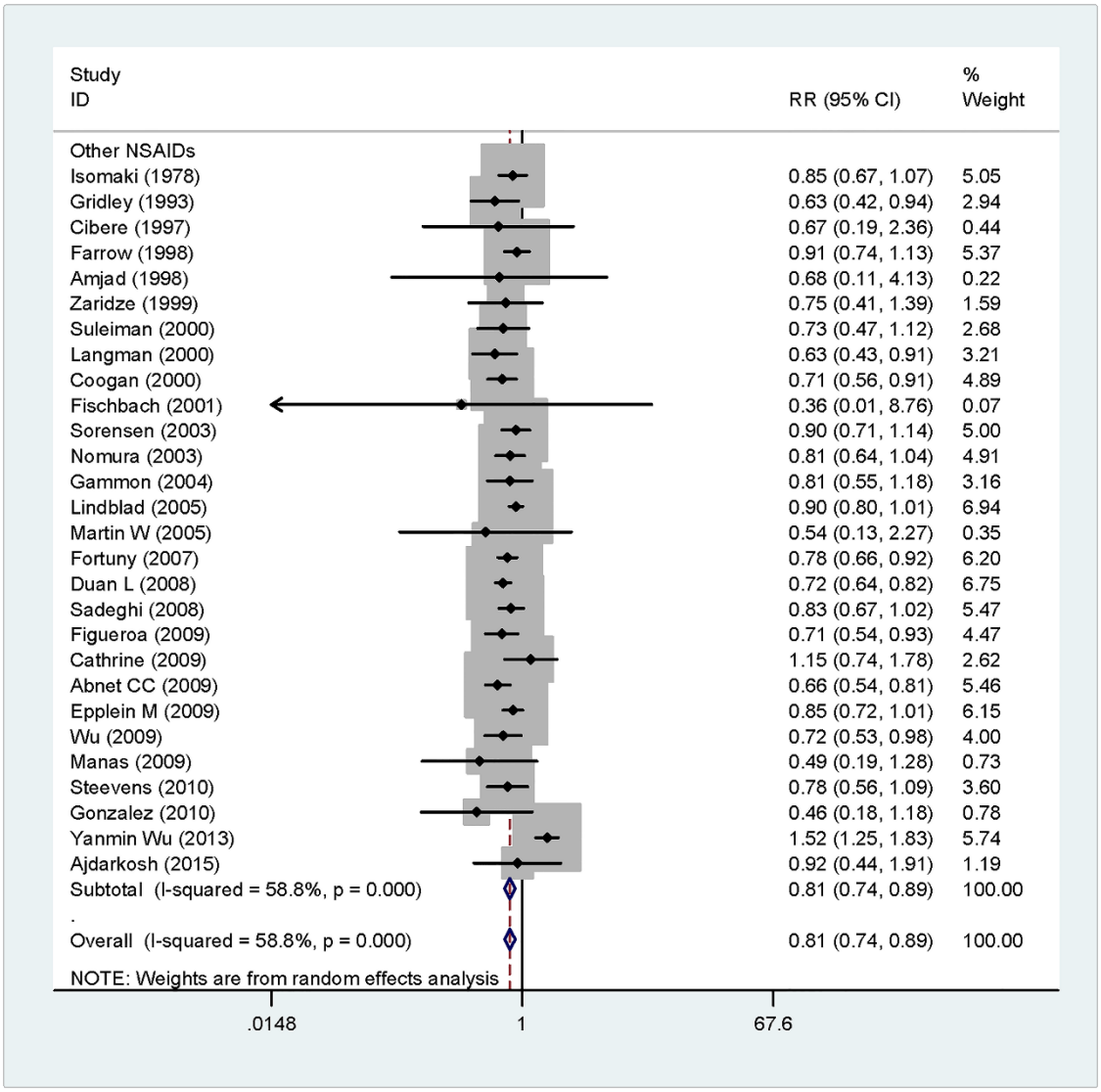
Supplementary Figure S4. Forest plot of subgroup analyses of anti-inflammatory drug intake and gastric cancer risk for celecoxib group. The pooled relative risk was achieved using fix-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with celecoxib intake.



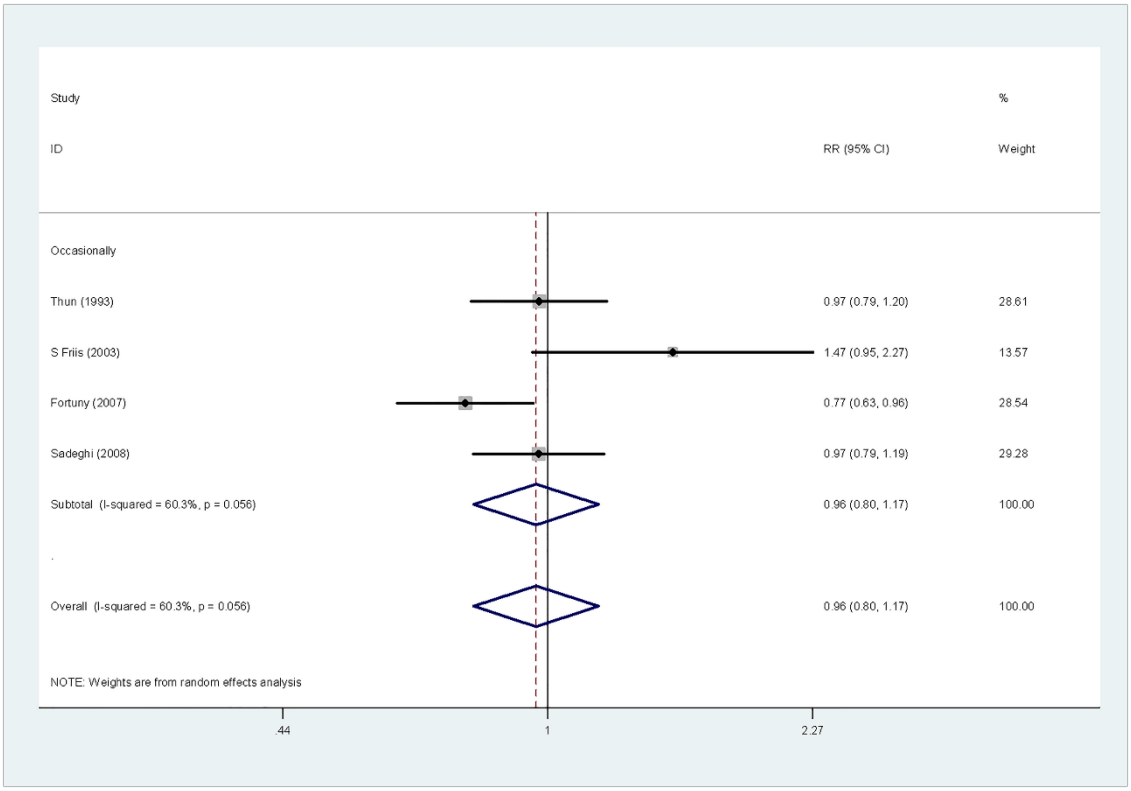
Supplementary Figure S5. Forest plot of subgroup analyses of anti-inflammatory drug intake and gastric cancer risk for COX-2 inhibitors group. The pooled relative risk was achieved using fix-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with COX-2 inhibitors intake.



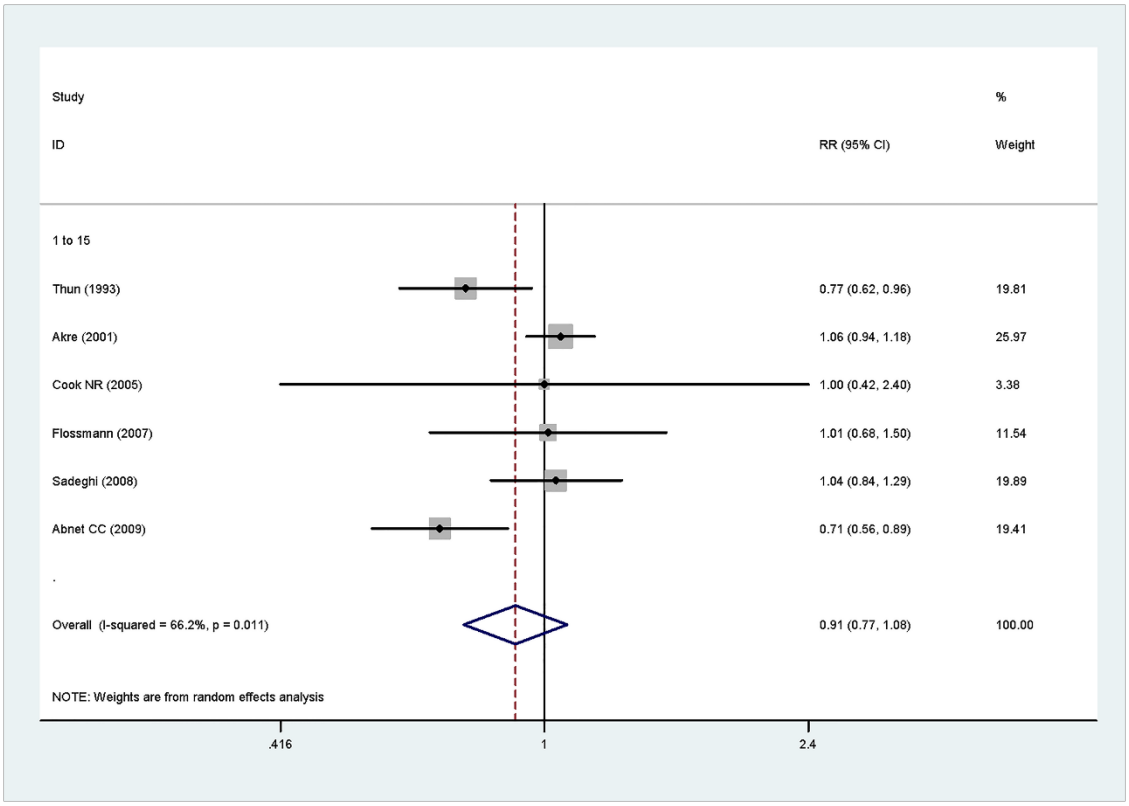
Supplementary Figure S6. Forest plot of subgroup analyses of anti-inflammatory drug intake and gastric cancer risk for other NSAIDs group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with other NSAIDs intake.



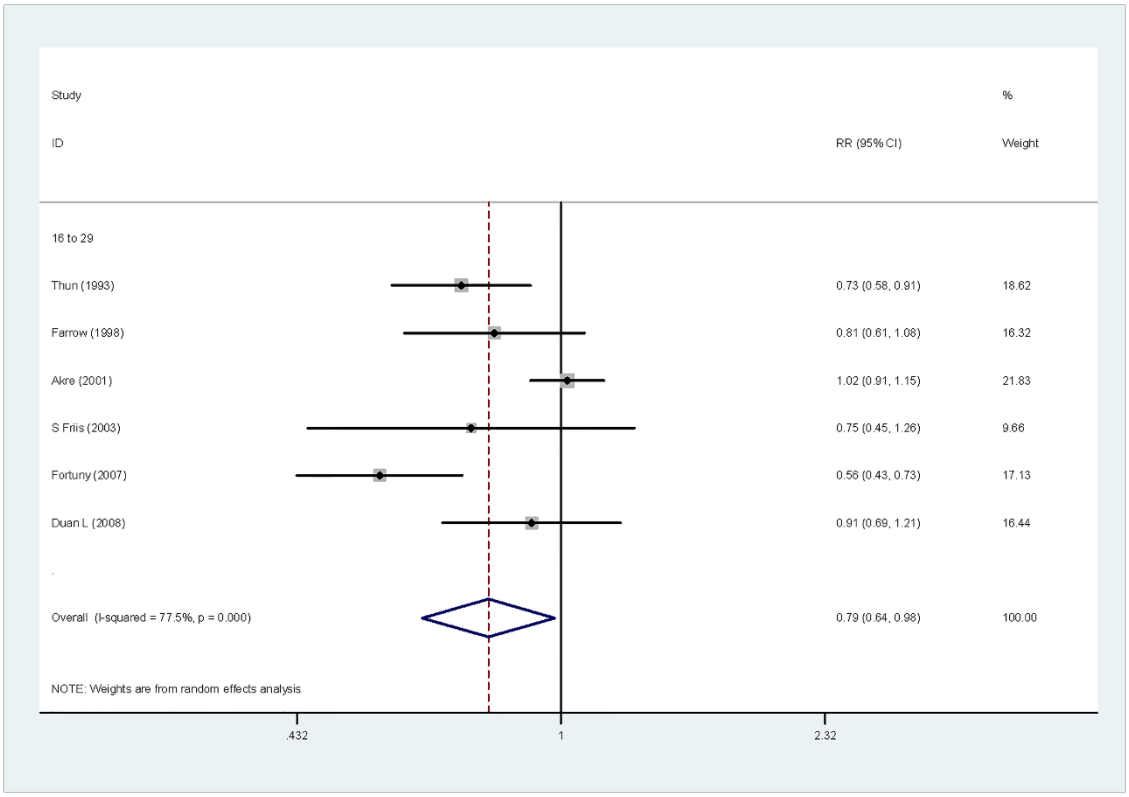
Supplementary Figure S7. Forest plot of subgroup analyses of aspirin intake and gastric cancer risk for the frequency of occasionally use group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with aspirin intake.



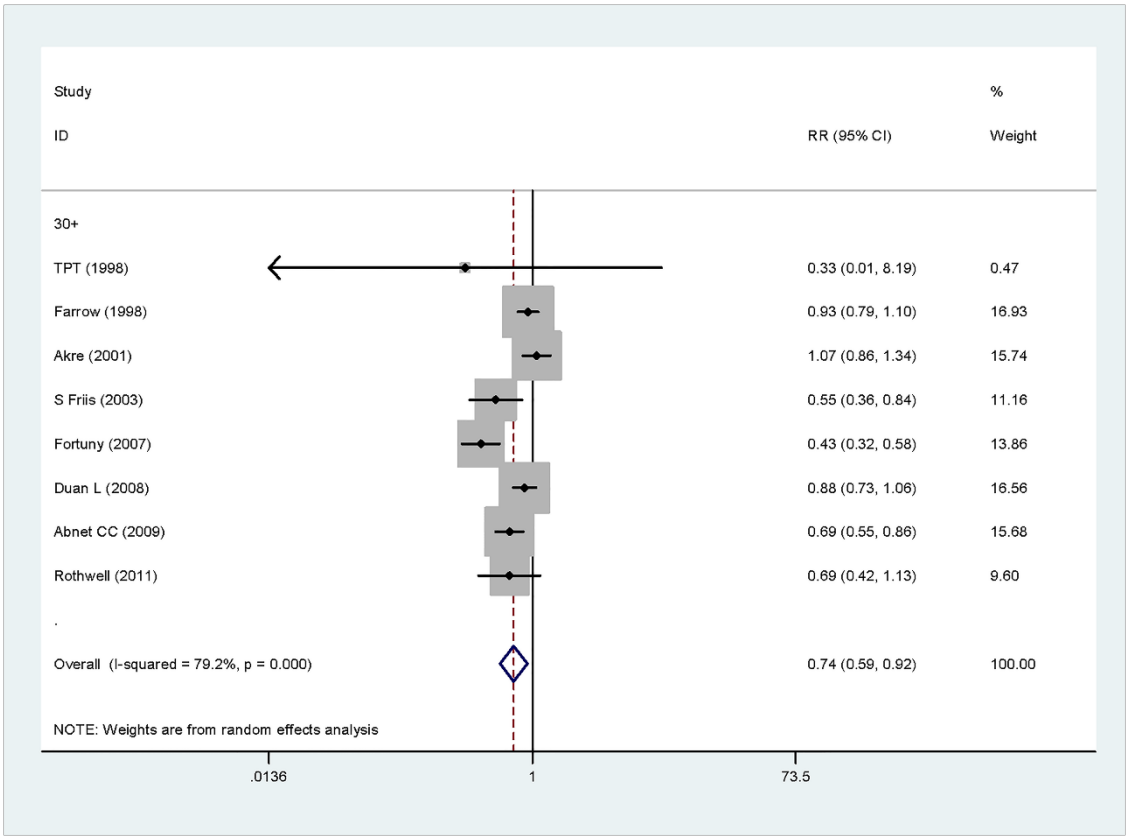
Supplementary Figure S8. Forest plot of subgroup analyses of aspirin intake and gastric cancer risk for the frequency of 1 to 15 times per month use group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with aspirin intake.



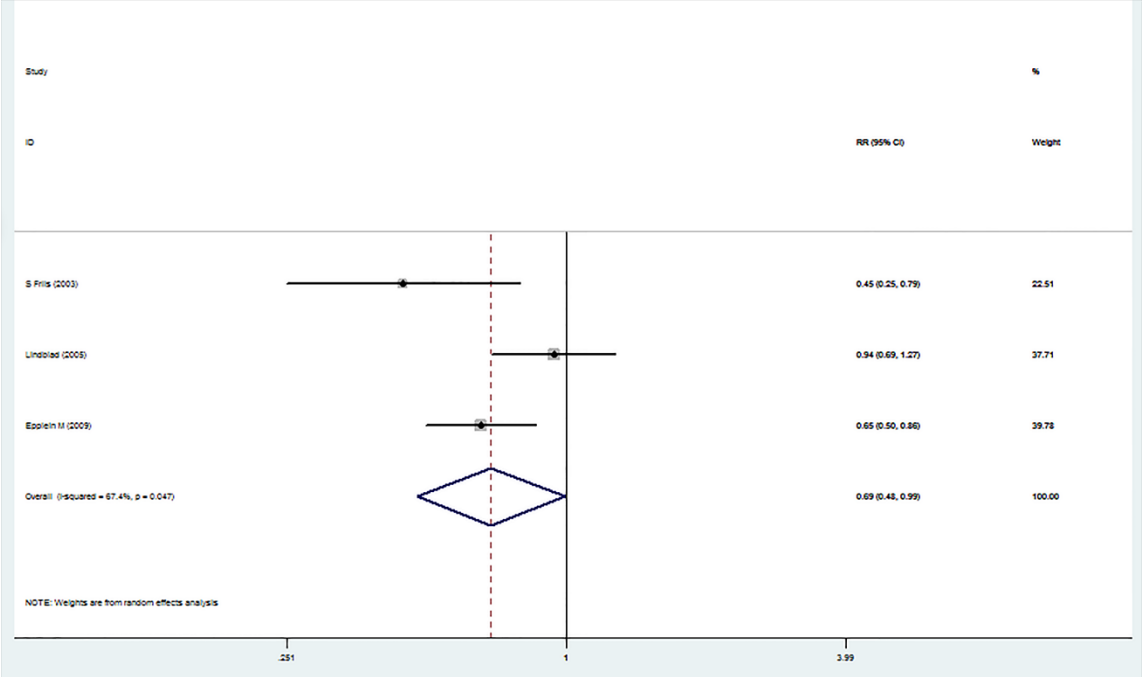
Supplementary Figure S9. Forest plot of subgroup analyses of aspirin intake and gastric cancer risk for the frequency of 16 to 29 times per month use group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with aspirin intake.



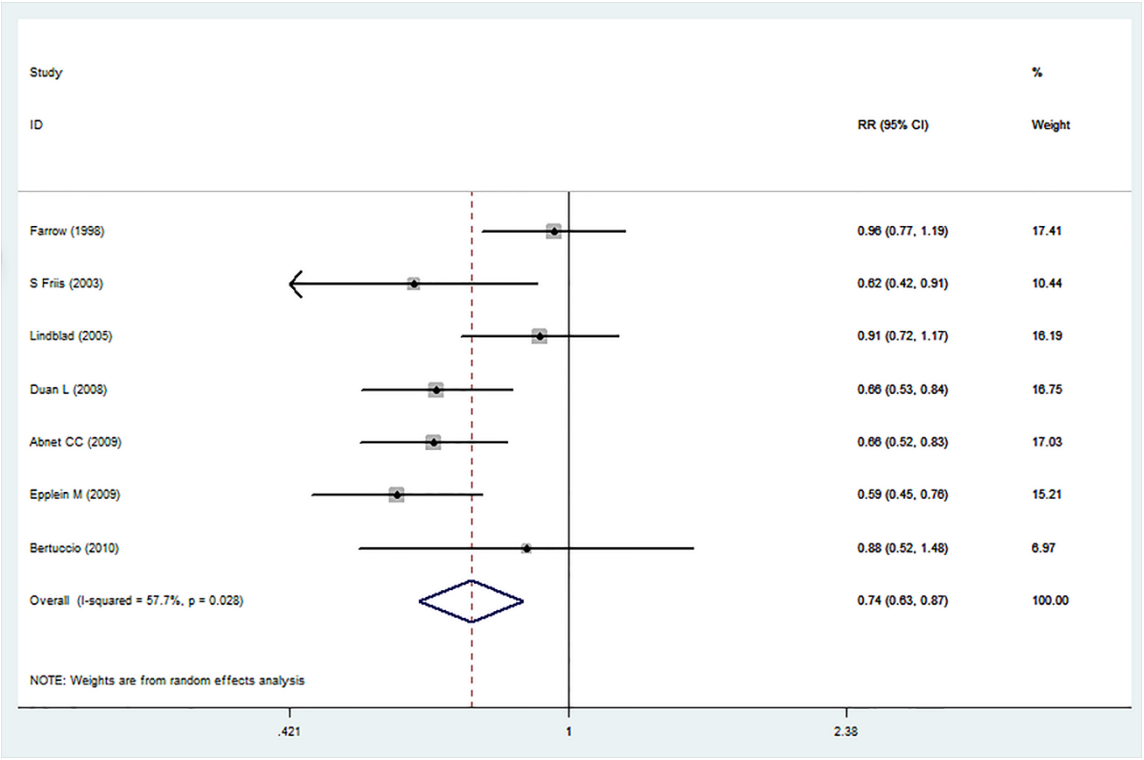
Supplementary Figure S10. Forest plot of subgroup analyses of aspirin intake and gastric cancer risk for the frequency of >30 times per month use group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with aspirin intake.



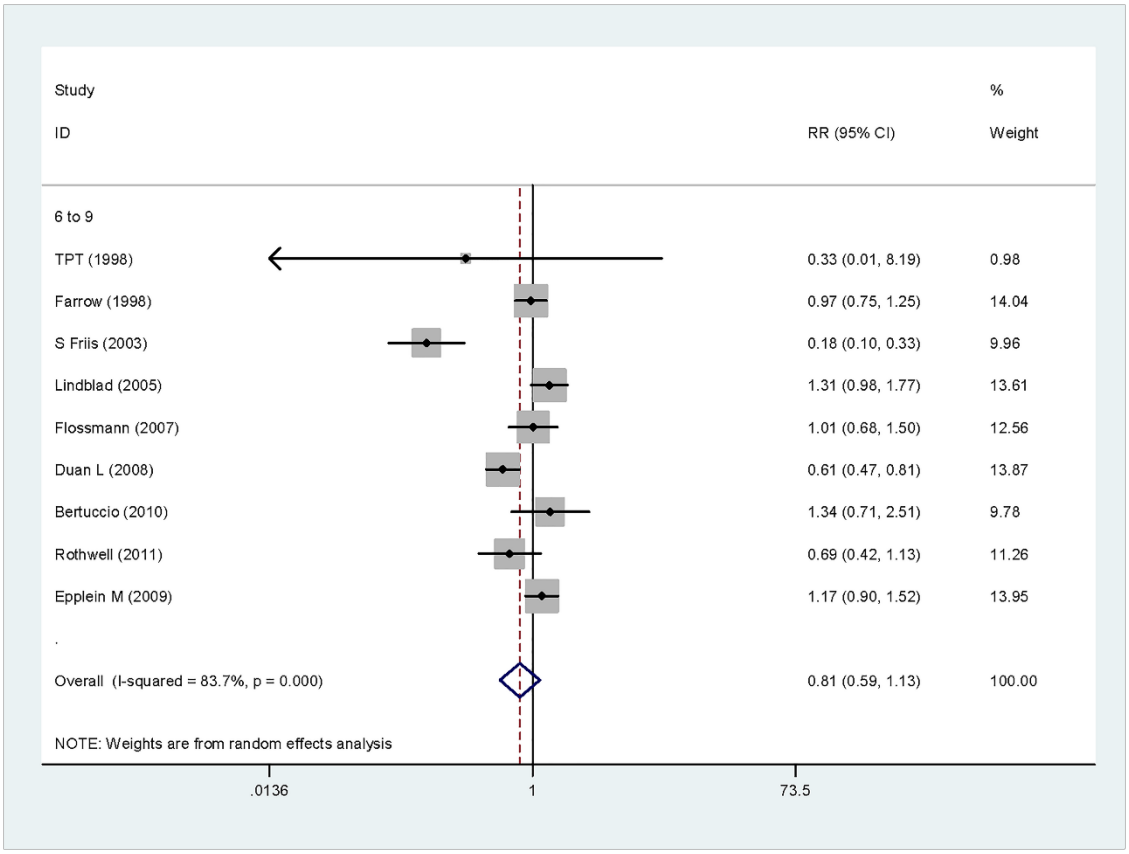
Supplementary Figure S11. Forest plot of subgroup analyses of aspirin intake and gastric cancer risk for the duration of ⩽1 years use group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with aspirin intake.



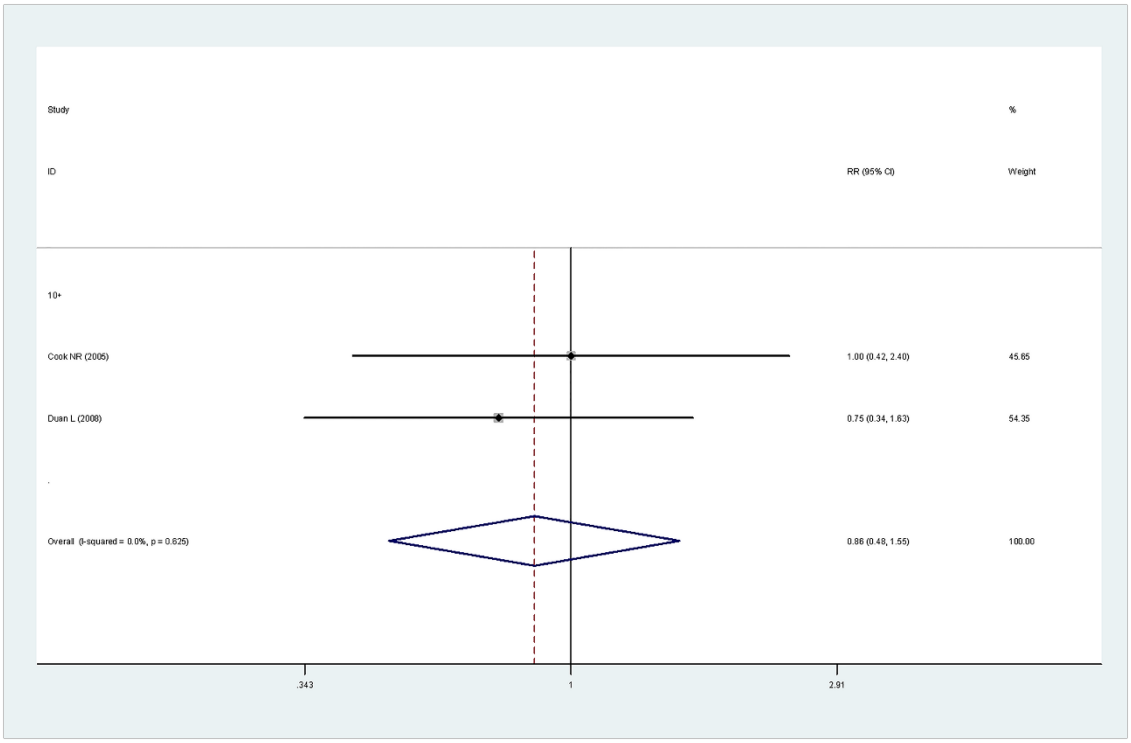
Supplementary Figure S12. Forest plot of subgroup analyses of aspirin intake and gastric cancer risk for the duration of 2 to 5 years use group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with aspirin intake.



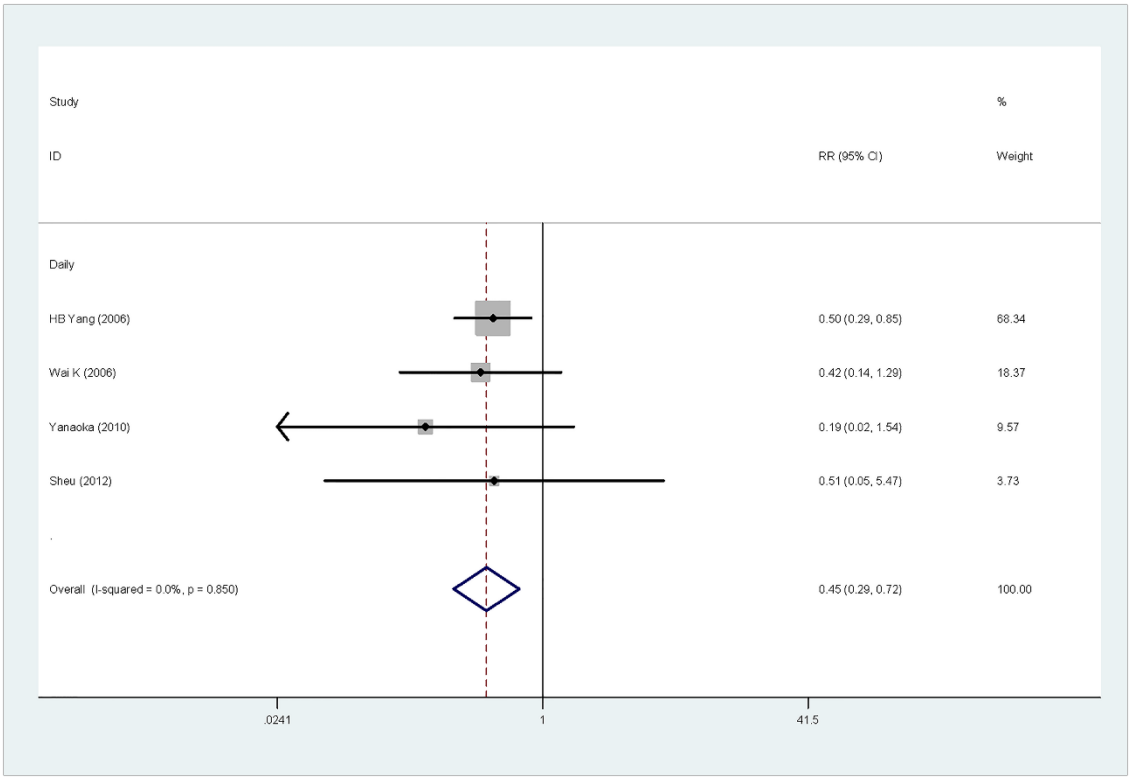
Supplementary Figure S13. Forest plot of subgroup analyses of aspirin intake and gastric cancer risk for the duration of 6 to 9 years use group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with aspirin intake.



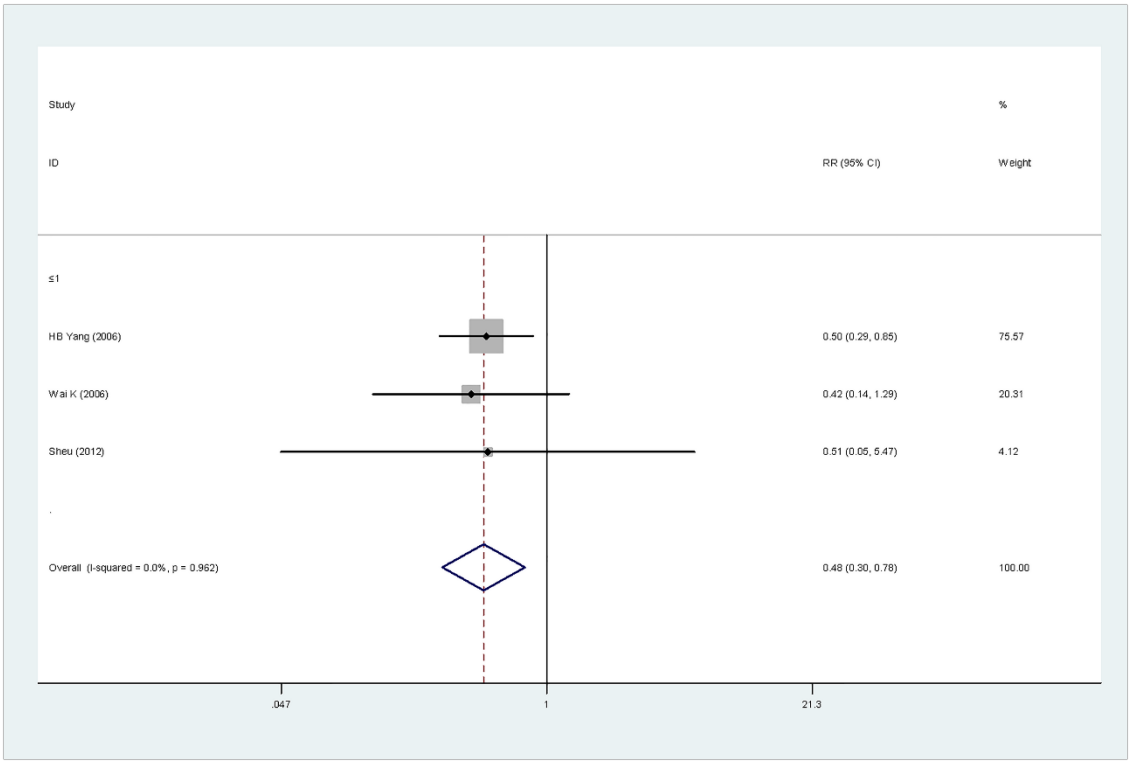
Supplementary Figure S14. Forest plot of subgroup analyses of aspirin intake and gastric cancer risk for the duration of >10 years use group. The pooled relative risk was achieved using fix-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with aspirin intake.



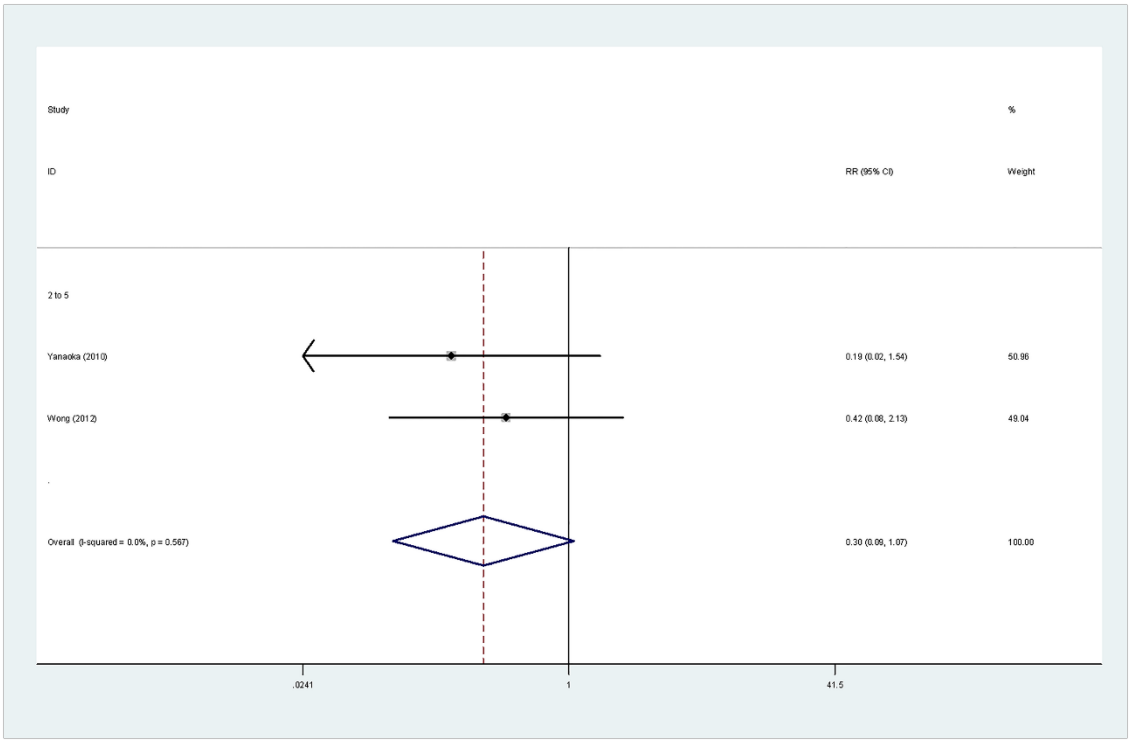
Supplementary Figure S15. Forest plot of subgroup analyses of COX-2 inhibitors intake and gastric cancer risk for the frequency of daily use group. The pooled relative risk was achieved using fix-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with COX-2 inhibitors intake.



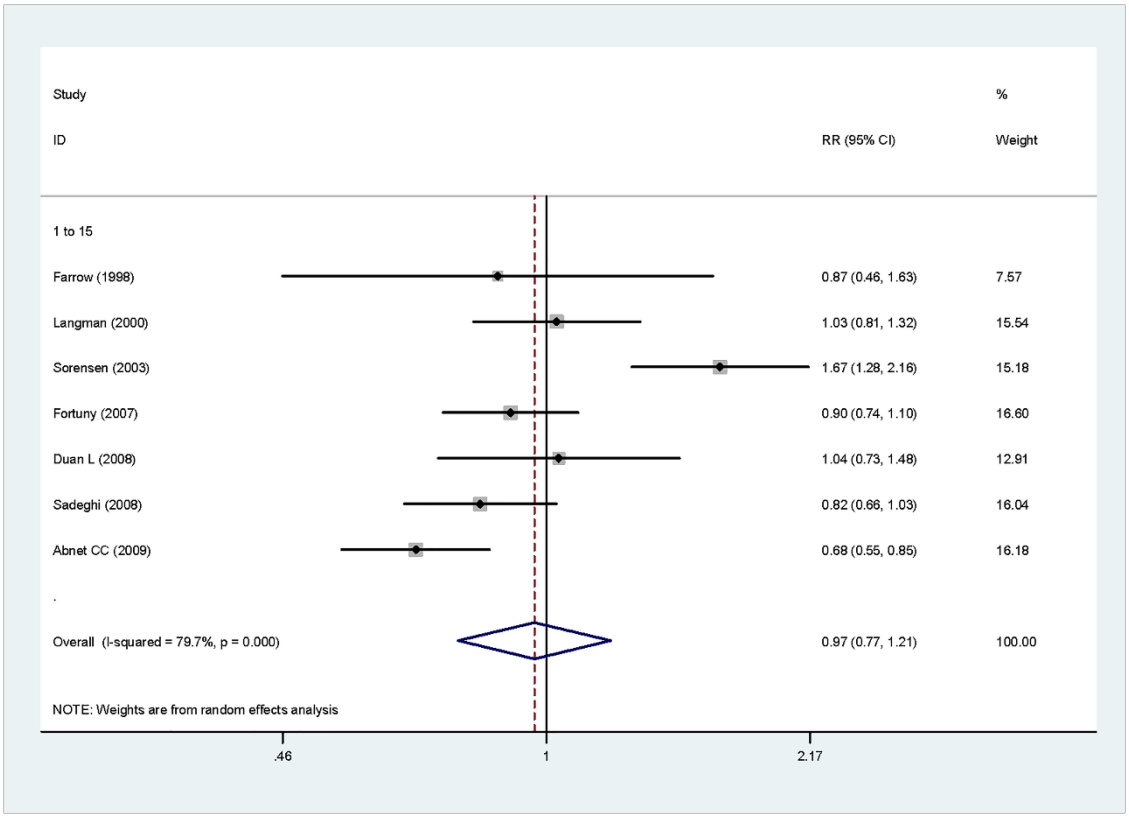
Supplementary Figure S16. Forest plot of subgroup analyses of COX-2 inhibitors intake and gastric cancer risk for the duration of ⩽1 year use group. The pooled relative risk was achieved using fix-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with COX-2 inhibitors intake.



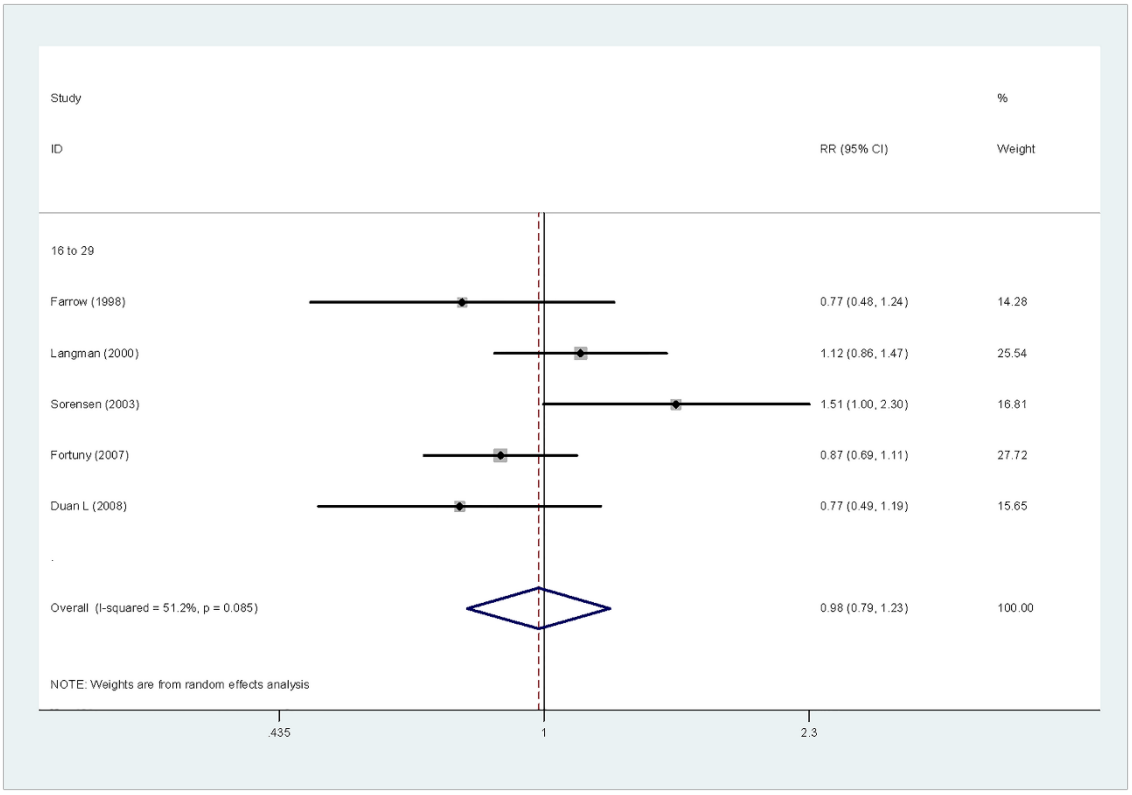
Supplementary Figure S17. Forest plot of subgroup analyses of COX-2 inhibitors intake and gastric cancer risk for the duration of 2 to 5 year use group. The pooled relative risk was achieved using fix-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with COX-2 inhibitors intake.



Supplementary Figure S18. Forest plot of subgroup analyses of other NSAIDs intake and gastric cancer risk for the frequency of 1 to 15 times per month use group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with other NSAIDs intake.



Supplementary Figure S19. Forest plot of subgroup analyses of other NSAIDs intake and gastric cancer risk for the frequency of 16 to 29 times per month use group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with other NSAIDs intake.



Supplementary Figure S20. Forest plot of subgroup analyses of other NSAIDs intake and gastric cancer risk for the frequency of >30 times per month use group. The pooled relative risk was achieved using random-effects model. Grey square represents relative risk in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. Squares or diamonds to the left of the solid vertical line indicate benefit with other NSAIDs intake.