SYSTEMATIC REVIEW AND META-ANALYSIS

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Aspirin and Reducing Risk of Gastric Cancer: Systematic Review and Meta-Analysis of the Observational Studies

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ABSTRACT

Background & Aims: The latest meta-analysis on the role of aspirin on various cancers was published in early 2018. By including the latest and updated primary observational studies, we aimed to conduct this systematic review and meta-analysis to synthesize stronger evidence on the role of aspirin in reducing gastric cancer (GC) risk.

Methods: The PubMed, Scopus, and MEDLINE databases were systematically searched up to December 2019 to identify relevant studies. Random-effects model was used to calculate summary ORs and 95%CI for I^2>50%. If the heterogeneity is not significant, the fixed-effects model was used. Overall analysis of the studies, inverse variance weighting after transforming the estimates of each study into log OR and its standard error were used.

Results: 21 studies were included in this meta-analysis. Results showed that aspirin significantly reduced the GC risk (OR=0.64, 95%CI=0.54-0.76) with substantial heterogeneity (I^2=96%). Effect of GC risk reduction in low dose (OR=0.80, 95%CI=0.59-1.09) is slightly greater than high dose aspirin (OR=1.08, 95%CI=0.77-1.52). Protective effect of aspirin uses >5 years (OR=0.67, 95%CI=0.34-1.31) was greater than <5 years (OR=1.01, 95%CI=0.72-1.43)

Conclusion: In conclusion, this meta-analysis showed that low dose aspirin with longer duration of more than 5 years were associated with a statistically significant reduction in GC risk. However, due to possible confounding variables and bias, these results should be cautiously treated.

Key words: aspirin – risk of gastric cancer – systematic review – meta-analysis – observational studies.

Abbreviations: GC: gastric cancer; NSAID: non-steroidal anti-inflammatory drug.

INTRODUCTION

Gastric adenocarcinoma, so called gastric cancer (GC) is the second most common gastrointestinal malignancy and it is the sixth common malignancy worldwide [1]. Although the incidence of GC in western countries has been decreasing, it remains one of the leading causes of cancer mortality worldwide [2]. According to 2019 Cancer Statistics report done by American Cancer Society, new cases of GC in 2019 were 27,510 and estimated deaths due to GC were 11,140 in both sexes [3].

Most of the environmental risk factors of GC are preventable with measures such as eradication of *Helicobacter pylori* infection, high intake of fresh fruits and vegetables, low-sodium diet, low red meat and sensible alcohol drinking [4-6]. In gastric carcinogenesis, inflammation plays an important role and anti-inflammatory therapy is efficacious towards early neoplastic progression and malignant conversion [7].

Aspirin has been known to have anti-inflammatory and chemo-preventive effect on various cancers including colorectal and gastric cancer [8, 9]. It is one of the effective non-steroidal anti-inflammatory drugs (NSAIDs) which inhibits the inflammation by suppression of cyclooxygenase (COX)-2 [10, 11].

Many systematic reviews and meta-analyses have assessed the role of aspirin in reducing cancer risk [12, 13]. However, those studies were on various types of cancer. As aspirin has been used for prevention of atherosclerosis and cardiovascular diseases, there were many primary observational studies both cohort and case-control types. Therefore, by including the latest and updated primary observational studies, we conducted this

systematic review and meta-analysis to synthesize stronger evidence on the role of aspirin in reducing GC risk.

METHODS

Literature search strategy

The systematic literature search was carried out according to "Preferred Reporting Items for Systematic Review and Meta-Analyses" (PRISMA) checklist [14] in three health-related databases (PubMed, Scopus, and MEDLINE). Search terms such as "gastric cancer", "stomach cancer", "gastric adenocarcinoma", "aspirin" and "reducing risk" were used to search for relevant studies. Terms from the categories were connected with "OR" within each category and by "AND" between categories. The search was limited to original articles published in the English language up to December 2019. To find out additional studies, reference lists of the original articles were screened through.

Inclusion and exclusion criteria

Inclusion criteria followed the PICOS format: Population (P), Interventions (I), Comparisons (C), Outcomes (O) and Study design (S) as follow: P: individuals without histologically confirmed GC; I: exposure of aspirin of any dosage and any duration; C: Aspirin user and non-aspirin user, aspirin user and other NSAID or placebo user; O: reduction of GC risk; S: observation studies (both case control and cohort studies.

Studies that did not meet the inclusion criteria were excluded. Review articles, case reports, editorials, and studies that used aspirin with combination of NSAIDs were excluded.

Data Extraction

Two investigators extracted the data independently and any disagreement was resolved by discussion. Data of the primary studies such as name of author, publication year, country, ethnicity, gender, age group, number of controls, number of cases, study design, aspirin dosage, duration of aspirin uses, site of GC, histological types of GC, odds ratio (OR), hazards ratio (HR) or relative risk (RR) with its 95% confidence interval (Cl) and any confounding factors in the analysis were extracted.

Assessment of Study Quality

The quality of eligible studies were assessed by the Newcastle-Ottawa Quality Assessment Scale [15]. Studies were assessed using three categories, selection of study groups (0-4 points), comparability (0-2 points), and exposure (0-3 points). A total score ≤ of 3 was considered low quality, scores between 4-6 moderate quality and scores ≥ 7 high quality. These scores were used only to facilitate the interpretation of the meta-analysis results, but not used as a criterion for inclusion or exclusion of the studies. During these processes, any discrepancy or disagreement was resolved by discussion to arrive consensus.

Data analysis

The meta-analysis was conducted to evaluate the effect of aspirin in reducing the GC risk. PRISMA checklist was employed for extraction data, analysis and reporting of observational studies. I^2 test was used to measure heterogeneity between these individual studies. Significant heterogeneity is indicated if $p<0.05$ and, or $I^2>50\%$ [15]. Some primary studies indicated raw data and some indicated only OR or RR. Therefore, for overall analysis of the studies, we used inverse variance weighting, after transforming the estimates of each study into log OR and its standard error. For subgroup analysis, as all studies for subgroups provided raw data, raw data of aspirin user and non-user were used.

A random-effects model was used to calculate summary ORs and 95%CI for $I^2>50\%$. However, if the heterogeneity was not significant, the fixed effects model was employed. Subgroup analysis were further administered based on cancer sites, dosage, gender, duration, ethnicity and histological types. In subgroup analysis, raw data were used as some primary studies indicated separate data for separate subgroups. In addition, funnel plots were carried out for evaluating bias risk of publication. For all the tests, two tailed p values were calculated, and it was considered as significant if p value was less than 0.05. All the meta-analysis tests were carried out by using RevMan 5.3 [16].

RESULTS

Literature search and study characteristic

A total of 5,675 studies were identified from three databases (3,529 from PubMed; 154 from Scopus; 1992 from Ebsco). A four-phase flow chart of the study selection process is illustrated in Fig. 1. PubMed Search string was Search ((((gastric cancer) OR stomach cancer) OR gastric adenocarcinoma) AND aspirin) AND reducing risk.

After excluding duplicate studies, animal studies, in vitro studies, case reports, reviews and other non-relevant studies, 563 studies were screened. After the title and abstract screening, 520 studies were excluded as those were studies on aspirin in treating GC cases and effects of aspirin on the progression, recurrence and survival of GC. Forty-six full-text papers were reviewed for eligibility and a final of 21 primary studies met the pre-specified inclusion criteria. A summary of the 25 excluded studies is provided in Supplementary Table I [17-41]. Table I indicates the characteristics of the included studies. Out of 21 included primary studies, 11 studies were case-control studies [42-52] and 10 were cohort studies [53-62]. Seven studies included in this meta-analysis were from the United States [44-47, 53, 55, 61], 5 were from Europe (one each from the United Kingdom, Sweden, Italy, Denmark and Russia) [42, 43, 50, 52, 56] and 9 from Asia countries (2 from Hong Kong, 4 from Korea, one from Taiwan, Japan and China) [39, 48, 49, 51, 57-60, 62]. The quality assessment of 25 included studies by using Newcastle-Ottawa Quality Assessment Scale is shown in Supplementary Table II.

Aspirin Use and GC

Twenty-one studies were included to evaluate the overall protective effect of aspirin. There was a significant inverse association between the case-control studies which seemed to have contributed to this significant overall effect compared to the cohort studies. However, there was a high heterogeneity (I^2=96%) (Fig. 2). The funnel plot (Fig. 3) showed some degree of publication bias. To overcome the heterogeneity, subgroup analyses (gender, ethnicity, duration of use, aspirin dosage, histological types and sites of GC) were carried out.

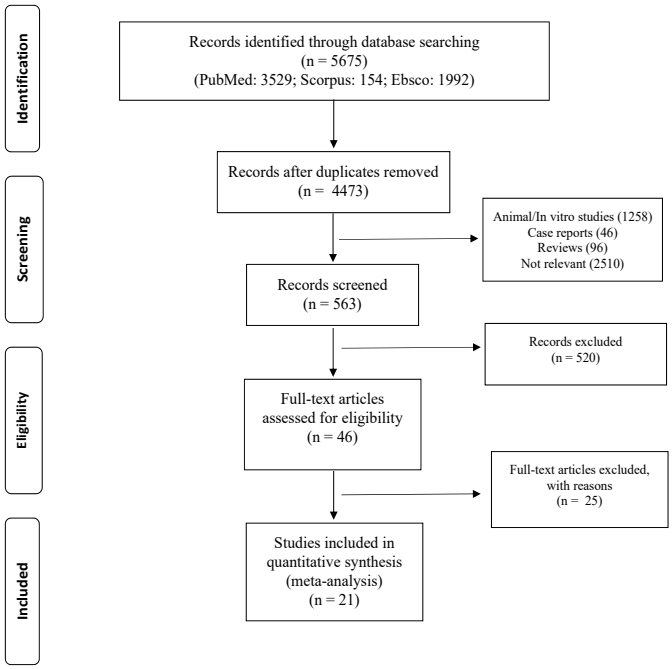

Fig. 1. PRISMA flow chart indicating study selection [14]

Subgroup analyses

The effect of gender on the use of aspirin and the risk of GC was examined in stratified analyses. Only three studies provided gender specific estimates. Inverse association between use of aspirin and GC risk was more in female (OR=0.66, 95%CI=0.45-0.97) than male (OR=0.86, 95%CI=0.62-1.20). However, there was substantial unexplained heterogeneity in the male group with I^2=59% and the differences in these subgroups were not statistically significant (p=0.31) (Fig 4A). The effect of ethnicity on the use of aspirin and risk of GC was examined in stratified analyses. Inverse association between aspirin use and the risk of GC was seen in the Caucasian population (OR=0.82, 95%CI=0.67-1.00). However, the differences in different ethnic subgroups were not statistically significant (p=0.11) (Fig. 4B).

In this study, two subgroups for the duration of aspirin use (<5 years and ≥5 years) were defined and the effect of these subgroups were stratified. Six studies provided duration specific estimates. Protective effect of GC by use of aspirin≥ 5 years (OR=0.67, 95%CI=0.34-1.31) was more than that of the duration <5 years (OR=1.01, 95%CI=0.72-1.43). However, duration subgroup differences were not statistically significant (p=0.29) although there was an overall heterogeneity of I^2=84% with p=<0.00001 (Fig. 5A).

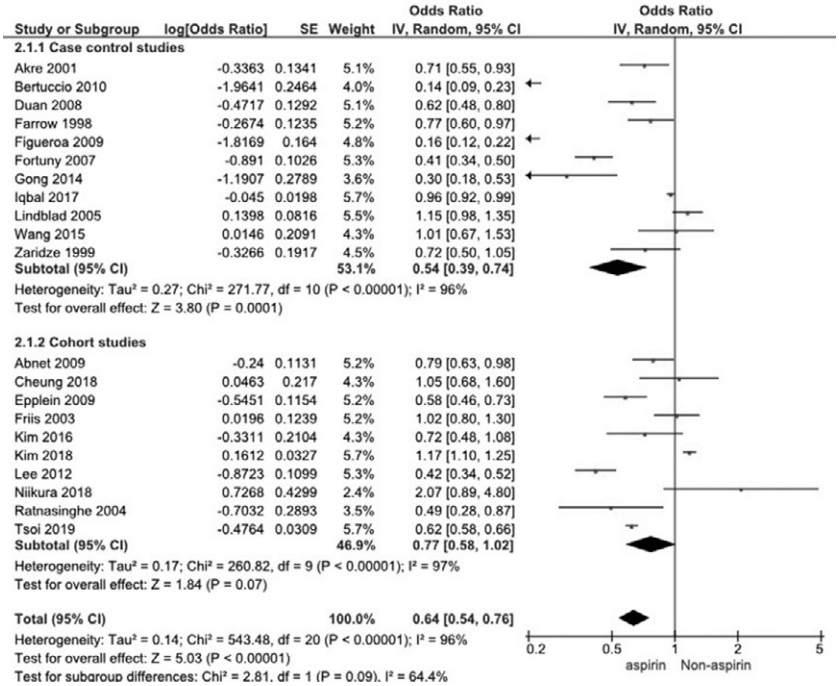

Fig. 2. Forest plot for the association between aspirin use and gastric cancer risk.

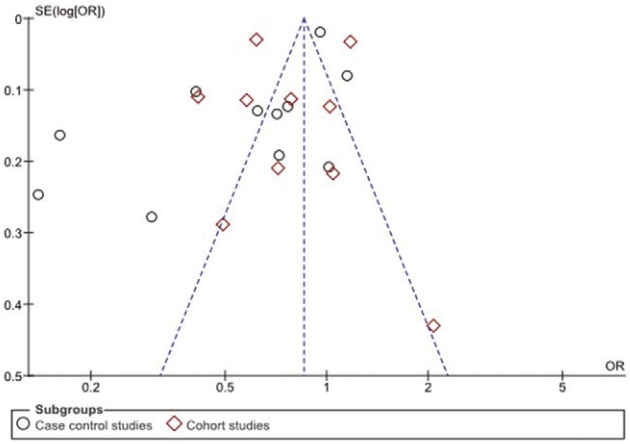

Fig. 3. Funnel plot showing the risk of bias publication.

Most of the included studies did not specifically report the dose; only three studies provided dose specific estimates. Less than 200 mg was considered as a low dose and more than 200 mg as high dose. There was no statistically significant difference between low dose and high dose aspirin in reducing the GC risk (p=0.21). However, it showed an inverse association between the effect of low dose aspirin and GC risk (OR=0.80, 95%CI=0.59-1.09) (Fig. 5B).

The possible association of GC risk in different histological type and use of aspirin was reported by three studies. There were no statistically significant association between aspirin use and histological types of GC (p=0.86). However, a slight inverse association between aspirin use and reduced risk of diffuse types of GC (OR=0.96, 95%CI=0.67-1.37) was seen (Fig. 6A). Five studies provided site (cardia and non-cardia) specific estimates of GC risk by the use of aspirin. These subgroup differences were not statistically significant (p= 0.10). However, there was a significant inverse association between aspirin use and non-cardia GC risk (OR=0.88, 95%CI=0.79-0.99) with heterogeneity (I^2=68%) (Fig. 6B).

DISCUSSION

The first report on the role of aspirin in cancer prevention was on colorectal cancer [63]. Since then, the cancer preventive role of aspirin has been evaluated. Several meta-analyses were performed on the association between the risk of GC and aspirin. Latest published meta-analysis studied the effect of aspirin on various cancers without any subgroup analysis [12]. Another meta-analysis published in 2017 investigated the role of aspirin together with other non-steroidal anti-inflammatory drugs on GC [64]. In the current study, the overall analysis showed that aspirin significantly reduced the GC risk. As this study was done on observational studies there were some degree of publication bias noted. Results of this study were similar with some previous meta-analyses [12, 13, 64-66]. Our results are discordant with one study [67] which claimed that aspirin decreased the chance of getting non-cardia GC only.

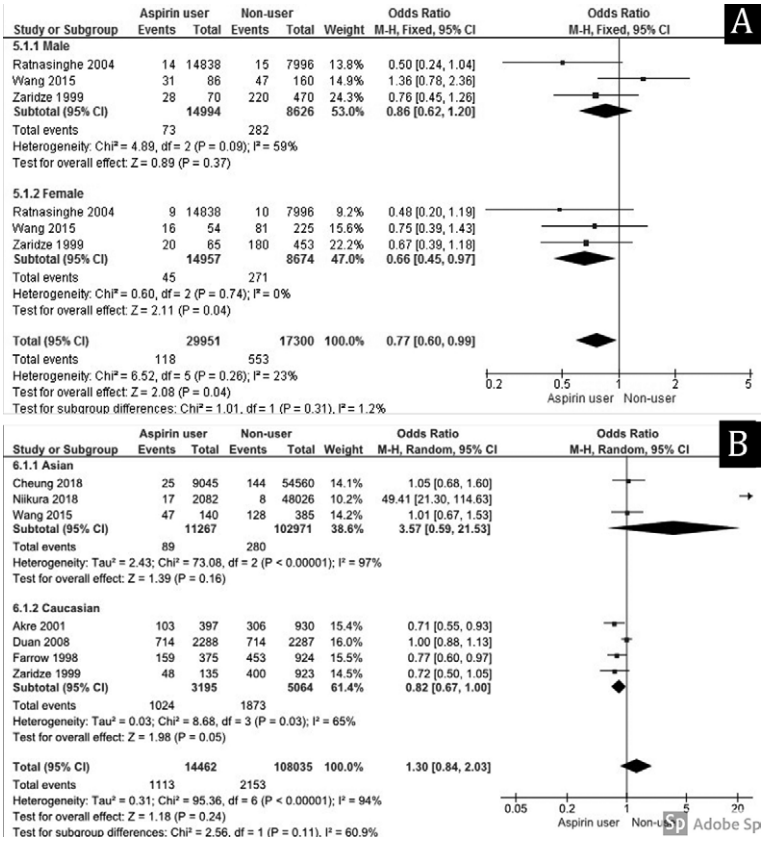

Fig. 4. (A) Forest plot for the association between aspirin use and GC risk in different sexes; (B) Forest plot for the association between aspirin use and different ethnicity.

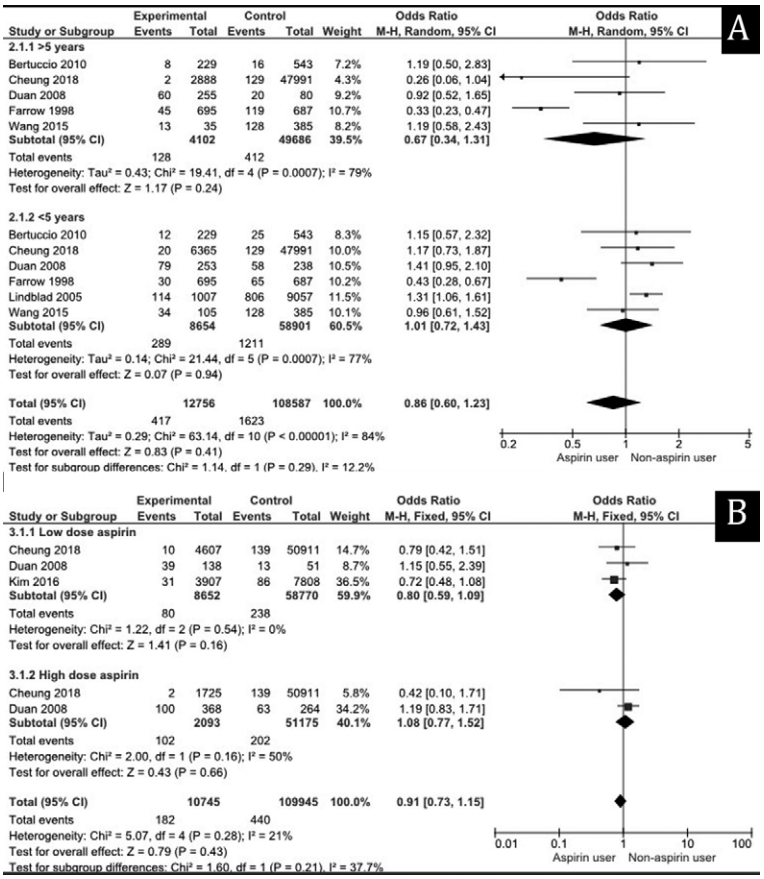

Fig. 5. (A) Forest plot for the association between duration of aspirin use and gastric cancer risk; (B) Forest plot for the association between dose of aspirin use and gastric cancer risk.

As the observational studies are more prone to publication bias [68, 69], there was some degree of publication bias noted in this meta-analysis. A study showed that the decreased risk of GC with aspirin was observed in the case-control studies, but not in the cohort studies [12]. However, a study indicated that both case-control studies (RR=0.84; 95%CI=0.70-1.00) and cohort studies (RR=0.81; 95%CI=0.67-0.98) showed an inversed relationship between the aspirin use and the risk of GC [65]. Some meta-analyses on aspirin and GC reported an inverse association [13, 64, 66] while another meta-analysis found no significant association [67] between the use of aspirin and GC risk.

As included studies were observational studies in this meta-analysis, the duration of observation was variable. Therefore, two groups for duration of aspirin use were defined: <5 years, and ≥5 years. Our results showed that the longer duration of aspirin use (≥5 years) has significantly reduced the risk of GC. However, pool estimate of duration subgroup differences was not statistically significant. Huang et al. [64] also reported that there were insignificant non-linear relationships between the duration of any NSAIDs use or aspirin use and GC risk. However, Kong et al [65] reported short or middle-term use (≤5 years) of aspirin was more effective in reducing GC risk.

In term of dose of aspirin use in this study, it showed that there is no statistically significant difference between low dose and high dose aspirin use in reducing GC risk (p=0.21). However, the inverse association between low dose aspirin use and reduced GC risk was noted. Most of the included primary studies did not specifically identify the dose and only a few studies identified it. However, we assumed that most studies on GC cases with follow up questioning on aspirin use were found to be of a low dose (1 to < 7 tablets per week). Kim et al [58] reported that defined daily dose (DDD)-year and cumulative dose >3 DDD-year has a reduced risk of GC. Huang et al. [64] reported there was a non-linear relationship between the frequency (dose) of aspirin use and GC risk. Low dose aspirin use is also associated with a reduced risk of other cancers such as colorectal, oesophagus and prostate cancer [12]. In general, as the definition of aspirin use and dosage varied among the included primary studies, statistically significant results on dose response was not found in this study.

Although gender subgroup analysis was not statistically significant in this study (p=0.31), significant inverse association between aspirin use and female GC risk was detected. Qiao et al. [12] reported no significant association with gender. Regarding ethnicity, there was an inverse association between the Caucasian population and a risk of GC compared to the Asian population. However, there was no statistically significant subgroup effect and most of the included studies are of Caucasian in this meta-analysis. Yang et al. [67] also reported that regular aspirin use was associated with a reduced risk of non-cardia GC among Caucasians.

There was no significant association of GC risk based on site and histological type with aspirin use in this study. However, an inverse association between aspirin use and non-cardia GC risk (OR=0.88, 95%CI=0.79-0.99) was noted. This finding is

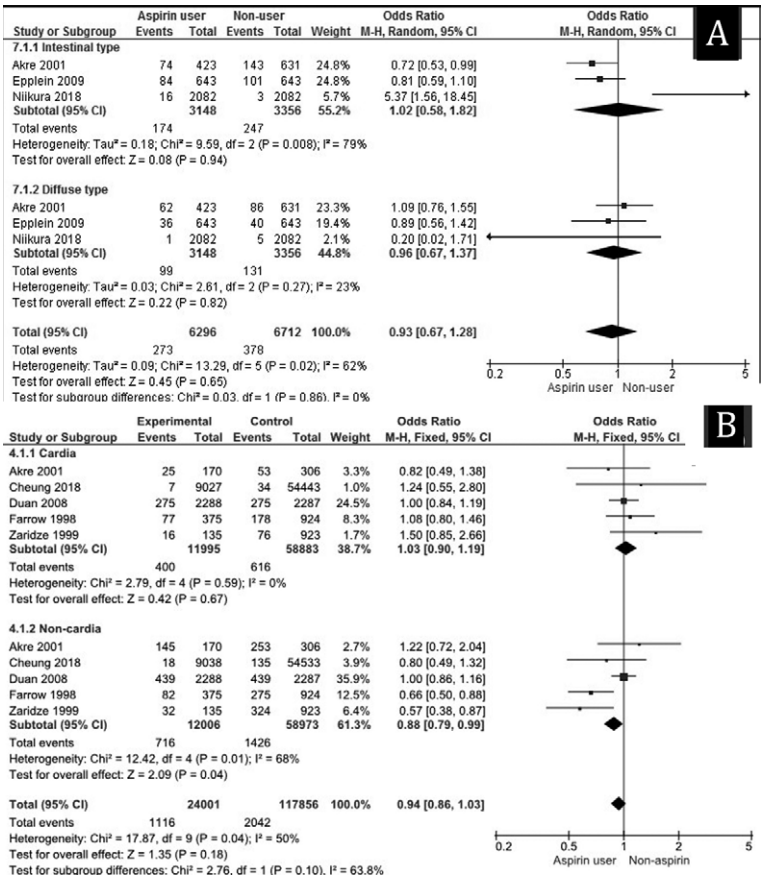

Fig. 6. (A) Forest plot for the association between aspirin use and different histological type of gastric cancer risk; (B) Forest plot for the association between aspirin use and the site of GC risk.

similar to some studies where it was reported that aspirin use was associated with only non-cardia GC but not with cardia GC [64, 67]. Niikura et al. [60] reported chemo preventive effect of aspirin is greater in diffuse types than intestinal types. In general, all the subgroup analyses in this study showed no statistically significant subgroup effects as all subgroup differences showed p-value > 0.1.

There were some limitations in this study especially in the subgroup analyses. Many studies did not specifically provide the duration of aspirin use. Duration and dose of aspirin use were not uniform in the included studies. Hence, more studies should be included and a larger sample size of population are required for better evidence towards the protective effect of aspirin on GC. However, many of the excluded studies reported on the combined effect of NSAIDs and aspirin rather than the effect of aspirin only.

CONCLUSION

This meta-analysis evidenced that low dose aspirin with a longer duration of more than 5 years was inversely associated with a significant reduction in GC risk. However, due to possible confounding variables and bias such as smoking and *Helicobater pylori* infection, these results should be cautiously treated.

Conflicts of interest: None to declare.

Authors' contribution: T.T.W. and S.N.A. conceived and designed the study. T.T.W., S.N.A., J.L.C.F., C.O.F. data analysis and interpretation. T.T.W drafted and revised the paper.

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Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-818

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