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Title

Safety and effectiveness of low-dose aspirin for the prevention of gastrointestinal cancer in adults without atherosclerotic cardiovascular disease: a population based cohort study

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Abstract

Objective

To assess whether low-dose aspirin use is associated with the incidence of colorectal cancer (CRC), gastric cancer (GC), and esophageal cancer (EC), and gastrointestinal bleeding (GIB) in people without established atherosclerotic cardiovascular disease.

Design

New-user, propensity score matched cohort study.

Setting

Clinical Data Analysis and Reporting System database, Hong Kong.

Participants

Adults ≥ 40 years who initiated low-dose aspirin (75-300 mg/daily) or paracetamol (non-aspirin users) between January 1, 2004 to December 31, 2008, without a history of atherosclerotic cardiovascular disease.

Main Outcome Measures

First diagnosis of gastrointestinal cancer (either CRC, GC, or EC). Secondary outcome was GIB. Individuals were followed from index date of prescription until the earliest occurrence of an outcome of interest, an incident diagnosis of any type of cancer besides the outcome, death, or until December 31, 2017. A competing risk survival analysis was used, with death as the competing risk to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results

After matching, 49 679 aspirin and non-aspirin users were included. The median (IQR) follow-up was 10.0 (6.4) years. Hazard ratios for low-dose aspirin compared with non-aspirin

users were 0.83 for CRC (95% confidence interval (CI) 0.76 to 0.91), GC (0.77, 95% CI 0.65 to 0.92]), and 0.88 for EC (0.67 to 1.16). However, low-dose aspirin use was significantly associated with an increased risk of GIB (HR 1.15, 95% CI 1.11 to 1.20), except for patients taking proton pump inhibitors or histamine H2-receptor antagonists (HR 1.03, 95% CI 0.96-1.10).

Conclusion

Low-dose aspirin was associated with a reduced risk of CRC (NNT 250) and GC (NNT 500), and an increased risk of GIB (NNH 125) in adults ≥ 40 years. However, among patients younger than 60 years or patients taking gastroprotective agents, there was no significant increase in the risk of GIB.

Keywords

Aspirin; gastrointestinal neoplasms; gastrointestinal hemorrhage, primary prevention

Article summary

Strengths and limitations of this study

- This is the first study to evaluate the association of low-dose aspirin with GI cancer and GIB among Chinese adults without a history of ASCVD.
- It is a population-wide cohort study with a large sample size, long duration of follow-up, and integrated health care system that captures aspirin prescriptions and cancer outcomes.
- Information on alcohol consumption, smoking status, and BMI, which could be associated with the outcome, was not available.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death with approximately 1.8 million new cases and 826,000 deaths worldwide in 2018.[1] The incidence of colorectal cancer is estimated to rise to 2.2 million people by 2030, with 1.1 million colorectal cancer associated deaths.[2] Apart from CRC, gastric cancer (GC) and esophageal cancer (EC) also pose a public health threat worldwide, with approximately 1 million and 600,000 new cases in 2018 respectively.[3]

Given the significant burden of gastrointestinal (GI) cancer, pharmacological intervention may play an important role in reducing the risk of GI cancer. The use of low-dose aspirin for GI cancers is controversial with different studies showing inconsistent results.[4-7] The US Preventative Services Task Force (USPSTF) currently recommends the initiation of low-dose aspirin for the primary prevention of cardiovascular disease (CVD) and CRC, only for patients aged between 50 to 69 years with ≥10% 10-year CVD risk without an increased bleeding risk.[8] A recent study showed that the protective effects of aspirin on CRC varied between ethnicities with the strongest association observed among Caucasians.[9] Furthermore, low-dose aspirin modestly increases the risk of gastrointestinal bleeding (GIB),[10] which might outweigh the GI cancer prevention benefits. The risk of GIB is especially a concern among the Chinese population as they are suspected to have a higher risk of bleeding.[11 12] Considering the possible variation in the protective effects of low-dose aspirin on GI cancer as well as in the risk of GIB, further studies conducted in the Asian population are warranted.

This study aimed to investigate the association of low-dose aspirin with the risk of colorectal cancer, gastric cancer, and esophageal cancer, in addition to the associated risk of GIB among individuals with no pre-existing atherosclerotic cardiovascular disease (ASCVD).

Methods

Data source

We used the Clinical Data Analysis and Reporting System (CDARS), which contains electronic patient records managed by the Hospital Authority (HA), a statutory body that manages all public hospitals and their clinics in Hong Kong. More than seven million Hong Kong residents have access to public healthcare services. CDARS stores clinical records from 1993 and has been used to conduct pharmacoepidemiologic studies, with high accuracy in coding with a positive value of approximately 90%.[13-18] The outcomes of this study (Positive predictive value: GIB, 100%; GI cancer, 100%) have been validated previously.[13-15]

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number: UW 18-033). Informed patient consent was not required as the data used in this study were anonymized.

Study design and patient selection

This was a population-wide retrospective cohort study between 2004 and 2017. Patients ≥40 years with a prescription of either low-dose aspirin (75-300 mg/daily) or paracetamol between January 1, 2004 and December 31, 2008 were identified. The date of the first low-dose aspirin or paracetamol prescription was considered the index date. To include new users of low-dose aspirin, patients with a prescription of aspirin one year prior to the index date were excluded. Patients diagnosed with any type of cancer, those who underwent a colectomy or gastrectomy, or diagnosed with ASCVD defined as ischemic heart disease, cerebrovascular disease, or peripheral artery disease before the index date were excluded. Nitrates and digoxin were used as proxies to indicate a history of ASCVD, hence, any patient with a nitrate or digoxin prescription in the year prior to the index date were also excluded **(Supplementary Table 1)**.

Patients who received paracetamol (non-aspirin users) were identified as the reference group for risk comparison. Paracetamol, which is prescribed commonly, was used to capture patients who have had contact with the healthcare system during the same time as the low-dose aspirin patients. Importantly, paracetamol is not indicated for any associated comorbidities and has no known association with any type of cancer. An intention-to-treat approach was adopted, where patients allocated to the low-dose aspirin group on the index date will remain in the low-dose aspirin group, and similarly for the non-aspirin group.

Outcomes

The primary outcomes of this study were the development of either colorectal cancer, gastric cancer, or esophageal cancer. The follow-up period started from the date of first prescription of either low-dose aspirin or paracetamol (i.e. index date) and was censored at the incident diagnosis of any cancer, death, or end of study period (December 31, 2017). Patients diagnosed with CRC, GC, and EC were identified using ICD-9 codes (International classification of diseases, 9th revision) **(Supplementary Table 1).** Secondary outcome was GIB that led to a hospital visit (in-patient, out-patient or A&E). The follow-up period started from the index date and was censored at diagnosis of the outcome, death or end of study period.

Study variables

Potential confounders included patient demographics (age, sex), comorbidities (diabetes mellitus, hyperlipidemia, hypertension, obesity, alcohol related disorders, congestive heart failure, arrhythmia and conduction disorders, arterial disease, valve disorders, cardiomyopathy, chronic kidney disease, hepatic failure, chronic obstructive pulmonary disease [COPD], thyroid disorders, schizophrenia, depression, bipolar disorder, peptic ulcer, gastrointestinal reflux, irritable bowel syndrome, inflammatory bowel syndrome, and bleeds

that led to hospitalization within one year prior to index date), and concomitant medication use one year prior to index date (nonsteroidal anti-inflammatory drugs [NSAIDs], antiplatelets, anticoagulants, oral hypoglycemic agents, insulin, diuretics, antihypertensive agents, anti-arrhythmic, calcium channel blockers, beta-blockers, angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor, peripheral vasodilators, lipid-lowering drugs, oral bisphosphonates, oral corticosteroids, proton pump inhibitors [PPI]/histamine-2 receptor blockers (H2-blockers), antidepressants, and antipsychotics).

Statistical analysis

Baseline characteristics of low-dose aspirin users and non-aspirin users were presented as frequencies (percentages) for categorical variables and as mean (±SD) for continuous variables. To reduce confounding arising from baseline differences between low-dose aspirin and non-aspirin users, propensity score (PS) matching was performed. Aforementioned confounders were included in estimating the PS value. Patients using low-dose aspirin and paracetamol were matched at a 1:1 ratio using a nearest neighbor algorithm with a caliper of 0.01. Standardized mean difference (SMD) <0.1 between treatment groups was considered acceptable/negligible.

The ratio of incidence per 1000-person years of CRC, GC, and EC among low-dose aspirin users and non-aspirin users was reported. The association of CRC, GC, and EC with the use of low-dose aspirin was estimated using competing risk Cox regression with death as the competing risk, and hazard ratio (HR) with 95% confidence interval (CI) was reported. The association of GIB with the use of low-dose aspirin was estimated using a Cox regression and HR with 95% CI was reported. The number needed to treat (NNT) and number needed to harm (NNH) was estimated using the equation; 1/absolute risk reduction and 1/absolute risk increase respectively.

Subgroup analysis was performed to investigate the risk of GI cancer and GIB in low-dose aspirin and non-aspirin users with different age groups (40-49 years old, 50-59 years old, 60-69 years old, 70-79 years old, and ≥80 years old). Since the use of gastroprotective agents (PPI/H2-blockers) could reduce the risk of GIB in patients on antithrombotic agents,[19] we assessed the association of GI cancer and GIB with the use of low-dose aspirin in patients on gastroprotective agents. As people with diabetes are at higher risk of developing cancer[20], we also evaluated the association of low-dose aspirin with GI cancer and GIB among this population. Lastly, the association between low-dose aspirin and GIB has been shown to be different depending on the location of the GIB. Therefore, we stratified the GIB outcome to upper GIB (UGIB) and lower GIB (LGIB).

Sensitivity analyses were conducted by excluding patients with cancer diagnosis during the first year of follow-up since the cancer could have developed before the start of follow-up. Patients with an ASCVD diagnosis during the first year of follow-up were removed to ensure all patients included have no pre-existing ASCVD. Non-aspirin users with a low-dose aspirin prescription during follow-up were censored at the first aspirin prescription. Lastly, the effectiveness of low-dose aspirin for GI cancer prevention was evaluated in patients taking low-dose aspirin for secondary ASCVD prevention; patients taking low-dose aspirin for primary and secondary ASCVD were included.

R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. The analyses were conducted by JS and cross-checked independently by JZ for quality assurance.

Patient and public involvement

There was no patient and public involvement.

Results

Baseline characteristics

We identified 324 568 aspirin and 420 000 non-aspirin users between January 1, 2004 and December 31, 2008. Following exclusion criteria, 428 159 patients were eligible for the PS matching **(Figure 1).** A total of 99 358 individuals (49 679 low-dose aspirin users and 49 679 matched non-aspirin users) were successfully matched. After matching, all baseline characteristics had SMD < 0.1 and were well-balanced. The mean (standard deviation [SD]) age for the cohort was 68.6 (12.6) years, and 48 022 (48.4%) were women **(Table 1).** The median (interquartile range [IQR]) follow-up for the cohort was 10.0 (6.4) years for the GI cancer outcome (9.8 [6.3] years low-dose aspirin users and 10.4 [6.3] years non-aspirin users), and 10.2 (5.9) years for the GIB outcome (9.9 [6.1] years low-dose aspirin users and 10.6 [5.7] years non-aspirin users)**.** The most common dose of aspirin was 80 mg daily (72.2%).

Risk of Gastrointestinal Cancer

In the propensity score-matched sample, 1954 of 99 358 participants developed CRC (876 low-dose aspirin users [1.7%] and 1078 non-aspirin users [2.2%]), 515 GC (222 [0.4%] and 293 [0.6%]), and 206 EC (96 [0.2%] and 110 [0.2%], respectively; **Table 2**). The number of patients who died due to CRC, GC and EC were 247 (28.2%), 99 (44.6%) and 51 (53.1%) in low-dose aspirin users respectively, and 360 (33.4%), 151 (51.5%) and 55 (50.0%) in non-aspirin users respectively. NNT is 250 and 500 for CRC and GC respectively, and the NNH is 125 for GIB.

The results from the competing risk survival analysis showed that low-dose aspirin use was significantly associated with a lower risk of CRC and GC compared to non-aspirin users

(CRC: HR, 0.83 [95% CI, 0.76-0.91]; GC: 0.77 [0.65-0.92]), but not with EC (HR, 0.88 [95% CI, 0.67-1.16]; **Table 2**). The association with lower risk was statistically significant for females (CRC: HR, 0.79 [95% CI, 0.68-0.90]; GC: 0.73 [0.54-0.98]) and males (CRC: HR, 0.86 [95% CI, 0.76-96]; GC: 0.79 [0.64-0.98]). The use of low-dose aspirin was significantly associated with a lower risk of CRC in patients aged between 70 to 79 years old (HR, 0.82 [95% CI, 0.71-0.94]) and among patients with diabetes (HR, 0.73 [95% CI, 0.57-0.94]), with a lower risk of GC among patients 80 years and older (HR, 0.60 [95% CI, 0.43-0.84]; **Table 2**).

There was no significant association between low-dose aspirin and esophageal cancer in any of the subgroup analysis (**Table 2**). The test for the interaction effect of low-dose aspirin and gastroprotective agents was not significant when assessing the association between low-dose aspirin and gastrointestinal cancer, with and without gastroprotective agents (*P* value for interaction, >0.5).

Risk of Gastrointestinal Bleeding

In the propensity score-matched sample, 10 629 of 99 358 participants had a GIB event (5498 low-dose aspirin users [11.1%] and 5131 non-aspirin users [10.3%]; **Table 3**). The number of patients who died due to GIB was 88 (1.6%) in low-dose aspirin users and 83 (1.6%) in non-aspirin users. Compared to non-aspirin users, low-dose aspirin was significantly associated with an increased risk of GIB (HR, 1.15 [95% CI, 1.11-1.20]). The association with higher risk was statistically significant for females (HR, 1.16 [95% CI, 1.10-1.23]) and males (HR, 1.15 [95% CI, 1.09-1.21]), in addition to patients aged 60 to 69 (HR, 1.13 [95% CI, 1.03-1.23]), 70 to 79 (HR, 1.44 [95% CI, 1.35-1.53]), and 80 years and older (HR, 1.18 [95% CI, 1.11-1.27].

Low-dose aspirin was not significantly associated with an increased risk of GIB in patients aged 40 to 49 (HR, 0.94 [95% CI, 0.77-1.15]) and 50 to 59 (HR, 1.05 [95% CI, 0.93-1.19]) as well as in patients with diabetes (HR, 1.07 [95% CI, 0.97-1.18]) and those taking gastroprotective agents (HR, 1.03 [95% CI, 0.96-1.10]; **Table 3**). The test for subgroup difference indicated significant difference between the association with and without gastroprotective agents (*P* value for interaction <0.001).

Low-dose aspirin was significantly associated with an increased risk of UGIB (HR, 1.14 [95% CI, 1.09-1.18]) and LGIB (HR, 1.31 [95% CI, 1.16-1.48]). The association with higher risk remained for LGIB among patients taking gastroprotective agents (HR, 1.70 [95% CI, 1.35-2.14]), however, low-dose aspirin was not associated with an increased risk of UGIB in those taking gastroprotective agents (HR, 0.98 [95% CI, 0.91-1.05]).

Sensitivity analysis

After removing patients with a cancer diagnosis during the first year of follow-up, the association remained similar for CRC (HR, 0.88 [95% CI, 0.80-0.96]), GC (HR, 0.76 [95% CI, 0.63-0.93]), and EC (HR, 1.13 [95% CI, 0.83-1.55]; **Figure 2).** The association with lower risk also remained after removing patients with a diagnosis of ASCVD during the first year of follow-up for CRC (HR, 0.90 [95% CI, 0.82-0.99]), GC (HR, 0.78 [95% CI, 0.66-0.94]), and EC (HR, 0.70 [95% CI, 0.53-0.94]). Lastly, the lower risk remained when censoring non-aspirin users at the first aspirin prescription during follow-up in CRC (HR, 0.88 [95% CI, 0.80-0.96]), and GC (HR, 0.80 [95% CI, 0.67-0.96]) but not EC (HR, 0.93 [95% CI, 0.71-1.23]). After combining all patients taking low-dose aspirin for either primary or secondary prevention of ASCVD, they had a lower risk of CRC (HR, 0.89 [95% CI, 0.83-0.96]), GC (HR, 0.78 [95% CI, 0.69-0.89]), as well as EC (HR, 0.73 [95% CI, 0.60-0.90]) compared to non-aspirin users.

Discussion

In Chinese adults without pre-existing ASCVD, our results suggest that the use of low-dose aspirin was associated with a lower risk of colorectal and gastric cancer compared to non-aspirin users during a median follow-up of 10 years. However, low-dose aspirin was associated with an increased risk of GIB. Nevertheless, a subgroup analysis showed that the use of low-dose aspirin was not associated with an increased risk of GIB among patients younger than 60 years old and those taking PPIs or H2-blockers.

Our findings are consistent with a meta-analysis of patient follow-up (maximum duration 20 years) from five randomized controlled trials which showed that aspirin was associated with a reduced risk of colorectal cancer (HR 0.76; 95% CI = 0.60-0.96).[21] In addition to RCTs, observational studies have also examined the association of low-dose aspirin with GI cancer.[22-29] Although studies have consistently shown a beneficial effect of using low-dose aspirin, findings from observational studies have largely been limited to Caucasians.[22 24-26 29] An earlier study in Hong Kong evaluated the risk of GIB and benefit of CRC reduction from the use of low-dose aspirin and found that low-dose aspirin lowered the risk of CRC but at the cost of a higher risk of GIB. The authors acknowledged that the results could be inaccurate due to indication bias since no comorbidities were used to adjust for baseline differences between aspirin and non-aspirin users.[30] Our present study adjusted for baseline differences between aspirin and non-aspirin users by incorporating the use of PS matching. Moreover, most studies include patients taking low-dose aspirin for both primary and secondary CVD prevention. However, the clinical implications for the primary prevention cohort is greater as initiating low-dose aspirin is no longer standard practice for this population.

A UK study has evaluated the protective effect of low-dose aspirin on CRC in a cohort with no pre-existing CVD.[4] However, the risk of GIB was not investigated. Nevertheless, the association of low-dose aspirin with a reduced risk of GI cancer was consistent with our findings. Furthermore, our findings are also consistent with our recent 13-year cohort study conducted in Hong Kong (N=74 161) which found that regular aspirin use was associated with a decrease in gastric cancer risk following *Helicobacter pylori* eradication.[14] Daily use, prolonged use, and use of a higher doses of aspirin after *Helicobacter pylori* eradication was associated with significant reduction in the risk of gastric cancer.[14]

The role of low-dose aspirin for the prevention of GI cancer is equivocal and questions remain, particularly for patients without a history of ASCVD. Some randomized controlled trials (RCTs) have reported no reductions in GI cancer incidence and mortality with the use of low-dose aspirin. [5 7] The Aspirin in Reducing Events in the Elderly (ASPREE) trial reported a higher mortality rate in patients taking low-dose aspirin compared to placebo. A secondary analysis showed cancer as the major contributor to the higher mortality rate (HR: 1.13; 1.10-1.56), with a subgroup analysis for GI cancer which detected no differences between groups (CRC: RR, 0.97 [0.77-1.24]).[6] Patients in the ASPREE trial were ≥70 years old, hence the benefits of low-dose aspirin for GI cancer prevention may be limited since most of the benefits of low-dose aspirin are apparent in studies of younger adults with longer duration of use.[31] Notably, Asians comprised only 1% of the trial population in ASPREE. Therefore, findings from ASPREE may be more applicable to healthy Caucasian adults.

Clinical implications

The finding that low-dose aspirin use was associated with a lower risk of CRC and GC is of particular clinical importance, especially among patients with no pre-existing ASCVD, since the decision to initiate low-dose aspirin is less well defined. GI cancers are major contributors

to mortality worldwide with no proven preventative treatment. Aspirin is affordable, easily accessible and has a recognized pharmacological profile which could be a means to improving the burden of disease. Additionally, the risk of GIB associated with low-dose aspirin is of particular interest in the Chinese population, which has a different bleeding profile compared to Caucasians.[12] Lastly, our study showed that for every 1000 patients taking low-dose aspirin, 6 GI cancer cases could be prevented, although it could cause 8 GIBs. However, the percentage of patients with GI cancer outcome who died was 30% to 50% compared to 1.6% for GIB. In addition, the percentage of fatal GIB (1.6%) is similar in both the low-dose aspirin and non-aspirin group. This indicates that the use of low-dose aspirin does not contribute to an increase in the risk of fatal GIB. Further, this is consistent with a meta-analysis published in 2016 which evaluated fatal GIB attributable to low-dose aspirin.[32] This information along with the knowledge that patients under 60 years or those taking gastroprotective agents are not at higher risk of GIB could assist with clinical decisions to initiate low-dose aspirin, irrespective of whether there is a history of cardiovascular disease.

Strengths and limitations

To our knowledge, this is the first study to evaluate the association of low-dose aspirin with GI cancer and GIB among patients without a history of ASCVD. A propensity score-matched cohort study emulates randomized controlled clinical trials and for this study which evaluates cancer as an outcome, the study design is appropriate as the feasibility of an RCT is low due to the long follow-up required. Furthermore, while low-dose aspirin is a non-prescription medication in Hong Kong, its cost is heavily subsidized ($15 HKD ~ $2 USD for 4-month supply) through the public healthcare system. Thus, misclassification of exposure to low-dose aspirin is likely minimal.[14]

This study has several limitations. Similar to other healthcare databases, information such as body mass index, smoking status, and alcohol consumption are not routinely recorded in CDARS. However, other confounders were used as proxy to account for these risk factors (COPD and alcohol related disorders). A general limitation of cohort studies is the unmeasured confounding effect which cannot be excluded. Finally, subgroup analyses by age, diabetes mellitus, and use of gastroprotective agents should be interpreted with caution as these are hypothesis generating since the low number of events upon stratification resulted in limited statistical power.

Our findings support a role for low-dose aspirin therapy for the prevention of colorectal and gastric cancer. Further research is needed to confirm the patient population that would derive the most benefit, and least harm, from taking low-dose aspirin.

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Data sharing

No additional data are available.

Author contributions

Dr. Chan and Ms. Shami had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Shami, Zhao, Chan, Wong.

Acquisition, analysis, or interpretation of data: Shami, Zhao, Pathadka, Wan, Chan, Wong.

Drafting of the manuscript: Shami

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Shami, Zhao, Wan.

Administrative, technical, or material support: Vora, Soriano-Gabarro, Wong, Chan.

Supervision: Chan, Wong.

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Conflict of interest

Dr Chan has received honorarium from the Hospital Authority and research funding from The Hong Kong Research Grants Council, The Research Fund Secretariat of the Food and Health Bureau, Narcotics Division of the Security Bureau of HKSAR, Hong Kong; National Natural Science Fund of China, China; Wellcome Trust, United Kingdom; Bristol-Myers Squibb, Pfizer, and Takeda, for work unrelated to this study. Professor Wong has received research funding outside the submitted work from the Hong Kong Research Grants Council and the Hong Kong Health and Medical Research Fund, National Institute for Health Research in the UK, European Commission, Amgen, Bayer, Bristol-Myers Squibb, GSK, and Janssen. Mr. Vora and Ms. Soriano-Gabarro are employees of Bayer AG. The remaining authors have no conflict of interest to declare.

Transparency declaration

Ms. Jessica Shami affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that

any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Jessica Shami

Dissemination declaration

Dissemination to study participants and or patient organizations is not possible.

License statement

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Tables

Table 1. Baseline Characteristics of Low-Dose Aspirin and Paracetamol Users[a]

Characteristics	Before Propensity Score Matching			After Propensity Score Matching		
	Low-dose Aspirin (n=60 869)	Paracetamol (n=367 290)	Standardized Difference [b]	Low-dose Aspirin (n=49 679)	Paracetamol (n=49 679)	Standardized Difference [b]
Age, mean (SD), y	69.1 (12.5)	57.6 (12.8)	0.912	68.0 (12.5)	69.1 (12.7)	0.09
Female	29 010 (47.7)	211 841 (57.7)	0.202	24 031 (48.4)	23 991 (48.3)	0.002
Aspirin dose						
≤100 mg	52 125 (85.6)	-	-	42 756 (86.1)	-	-
101 mg – 200 mg	7396 (12.2)	-	-	5909 (11.9)	-	-
200 mg – 300 mg	1348 (2.2)	-	-	1014 (2.0)	-	-
Medical conditions						
Hypertension	12 679 (20.8)	18 469 (5.0)	0.485	8651 (17.4)	8626 (17.4)	0.001
Congestive heart failure	3676 (6.0)	1568 (0.4)	0.321	1734 (3.5)	1289 (2.6)	0.05
Arrhythmia and conduction disorders	8397 (13.8)	3563 (1.0)	0.506	3915 (7.9)	2900 (5.8)	0.08
Arterial disease	601 (1.0)	578 (0.2)	0.110	378 (0.8)	321 (0.6)	0.01
Valve disorders	436 (0.7)	579 (0.2)	0.085	266 (0.5)	254 (0.5)	0.003
Cardiomyopathy	329 (0.5)	149 (0.0)	0.093	165 (0.3)	114 (0.2)	0.02
Diabetes mellitus	9079 (14.9)	12 148 (3.3)	0.412	6079 (12.2)	5975 (12.0)	0.006
Hyperlipidemia	2130 (3.5)	2662 (0.7)	0.194	1400 (2.8)	1325 (2.7)	0.009
Thyroid disorders	1189 (2.0)	4644 (1.3)	0.055	851 (1.7)	837 (1.7)	0.002
Major bleeding	408 (0.7)	1269 (0.3)	0.046	316 (0.6)	343 (0.7)	0.007
COPD	2868 (4.7)	6214 (1.7)	0.172	2062 (4.2)	2109 (4.2)	0.005
Obesity	214 (0.4)	358 (0.1)	0.054	139 (0.3)	144 (0.3)	0.002
CKD	1359 (2.2)	1343 (0.4)	0.165	801 (1.6)	737 (1.5)	0.01
Chronic liver disease	544 (0.9)	1953 (0.5)	0.043	437 (0.9)	462 (0.9)	0.005
GERD	150 (0.2)	410 (0.1)	0.032	105 (0.2)	115 (0.2)	0.004

Irritable bowel syndrome	45 (0.1)	293 (0.1)	0.002	37 (0.1)	41 (0.1)	0.003
Peptic ulcer	244 (0.4)	952 (0.3)	0.025	193 (0.4)	186 (0.4)	0.002
Inflammatory bowel disease	11 (0.0)	106 (0.0)	0.007	10 (0.0)	8 (0.0)	0.003
Alcoholism	1166 (1.9)	3005 (0.8)	0.095	826 (1.7)	836 (1.7)	0.002
Schizophrenia	1125 (1.8)	5699 (1.6)	0.023	900 (1.8)	916 (1.8)	0.002
Bipolar disorder	95 (0.2)	706 (0.2)	0.009	87 (0.2)	98 (0.2)	0.005
Depression	1158 (1.9)	6291 (1.7)	0.014	943 (1.9)	942 (1.9)	<0.001
Medications						
Diuretics	14 350 (23.6)	28 961 (7.9)	0.441	10 042 (20.2)	10 136 (20.4)	0.005
ACE inhibitor or ARB	16 819 (27.6)	20 267 (5.5)	0.623	11 195 (22.5)	11 003 (22.1)	0.009
Other antihypertensives	8785 (14.4)	18 471 (5.0)	0.321	6384 (12.9)	6676 (13.4)	0.02
CCB	22 514 (37.0)	45 062 (12.3)	0.599	16 622 (33.5)	17 637 (35.5)	0.04
Anti-arrhythmic	1562 (2.6)	1335 (0.4)	0.184	760 (1.5)	537 (1.1)	0.04
Beta-blockers	21 756 (35.7)	42 667 (11.6)	0.592	15 777 (31.8)	16 466 (33.1)	0.03
Peripheral vasodilators	741 (1.2)	598 (0.2)	0.128	435 (0.9)	373 (0.8)	0.01
Oral hypoglycemic	14 789 (24.3)	25 443 (6.9)	0.493	10 799 (21.7)	11 260 (22.7)	0.02
Insulin	3321 (5.5)	2686 (0.7)	0.275	1972 (4.0)	1790 (3.6)	0.02
Lipid lowering drugs	10 680 (17.5)	10 362 (2.8)	0.502	7019 (14.1)	6835 (13.8)	0.01
PPI or H2-blockers	21 143 (34.7)	39 028 (10.6)	0.601	14 323 (28.8)	13 898 (28.0)	0.02
NSAID	8324 (13.7)	62 026 (16.9)	0.089	7137 (14.4)	7503 (15.1)	0.02
Oral bisphosphonates	245 (0.4)	455 (0.1)	0.054	182 (0.4)	186 (0.4)	0.001
Oral corticosteroids	7561 (12.4)	30 915 (8.4)	0.131	5913 (11.9)	6136 (12.4)	0.01
Anticoagulants	2537 (4.2)	1359 (0.4)	0.257	1278 (2.6)	962 (1.9)	0.04
Antiplatelet	1408 (2.3)	328 (0.1)	0.205	532 (1.1)	316 (0.6)	0.05
Antipsychotics	2172 (3.6)	7718 (2.1)	0.088	1664 (3.3)	1708 (3.4)	0.005
Antidepressants	2583 (4.2)	10 947 (3.0)	0.068	2063 (4.2)	2110 (4.2)	0.005

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitors.

[a] Values are expressed as frequency (%) unless otherwise specified. [b] Standardized difference indicates difference in mean or proportion of covariates in the low-dose aspirin group vs the paracetamol group divided by the pooled standard deviation.

Table 2. Risk of Gastrointestinal Cancers with Low-Dose Aspirin and Paracetamol After Propensity Score Matching

	Low-dose Aspirin			Paracetamol				
	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	HR (95% CI)	*P* Value
Colorectal cancer	49 679	876/428 554	2.04	49 679	1078/457 195	2.36	0.83 (0.76-0.91)	<.001
Female	24 031	356/211 588	1.68	23 991	463/226 257	2.05	0.79 (0.68-0.90)	<.001
Male	25 648	520/216 966	2.40	25 688	615/230 938	2.66	0.86 (0.76-0.96)	.01
40-49 years old	4344	15/45 459	0.33	4002	26/44 565	0.58	0.57 (0.30-1.06)	.08
50-59 years old	9350	90/95 162	0.95	8416	105/91 025	1.15	0.84 (0.63-1.11)	.20
60-69 years old	11 489	224/110 070	2.04	11 050	250/112 834	2.22	0.89 (0.74-1.07)	.19
70-79 years old	14 976	352/123 565	2.85	15 326	446/139 167	3.20	0.82 (0.71-0.94)	.004
≥80 years old	9520	195/54 298	3.59	10 885	251/69 604	3.61	0.89 (0.74-1.07)	.23
Diabetes Mellitus	6079	108/46 923	2.30	5975	147/49 238	2.99	0.73 (0.57-0.94)	.01
PPI/H2 blocker use	14 323	224/112 848	1.98	13 898	262/120 357	2.18	0.85 (0.71-1.02)	.07
Gastric cancer	49 679	222/428 554	0.52	49 679	293/457 195	0.64	0.77 (0.65-0.92)	.003
Female	24 031	73/211 591	0.35	23 991	103/226 259	0.46	0.73 (0.54-0.98)	.04
Male	25 648	149/216 969	0.69	25 688	190/230 940	0.82	0.79 (0.64-0.98)	.03
40-49 years old	4344	5/45 459	0.11	4002	8/44 565	0.18	0.58 (0.19-1.77)	.34
50-59 years old	9350	31/95 162	0.33	8416	21/91 025	0.23	1.40 (0.80-2.45)	.24
60-69 years old	11 489	41/110 070	0.37	11 050	52/112 834	0.46	0.78 (0.51-1.17)	.22
70-79 years old	14 976	93/123 565	0.75	15 326	113/139 167	0.81	0.85 (0.65-1.12)	.26
≥80 years old	9520	52/54 298	0.96	10 885	99/69 604	1.42	0.60 (0.43-0.84)	.003
Diabetes Mellitus	6079	28/46 923	0.60	5975	40/49 238	0.81	0.69 (0.43-1.13)	.14
PPI/H2 blocker use	14 323	65/112 848	0.58	13 898	82/120 357	0.68	0.77 (0.56-1.07)	.12
Esophageal cancer	49 679	96/428 554	0.22	49 679	110/457 195	0.24	0.88 (0.67-1.16)	.37
Female	24 031	23/211 591	0.11	23 991	29/226 259	0.13	0.80 (0.46-1.39)	.43

Male	25 648	73/216 969	0.34	25 688	81/230 940	0.35	0.91 (0.66-1.25)	.55
40-49 years old	4344	2/45 459	0.04	4002	1/44 565	0.02	2.05 (0.22-19.5)	.53
50-59 years old	9350	11/95 162	0.12	8416	11/91 025	0.12	0.95 (0.41-2.19)	.90
60-69 years old	11 489	30/110 070	0.27	11 050	25/112 834	0.22	1.19 (0.70-2.02)	.53
70-79 years old	14 976	35/123 565	0.28	15 326	39/139 167	0.28	0.92 (0.58-1.45)	.72
≥80 years old	9520	18/54 298	0.33	10 885	34/69 604	0.49	0.61 (0.34-1.07)	.08
Diabetes Mellitus	6079	13/46 923	0.28	5975	19/49 238	0.39	0.67 (0.33-1.36)	.27
PPI/H2 blocker use	14 323	28/112 848	0.25	13 898	29/120 357	0.24	0.94 (0.56-1.58)	.82

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitors.

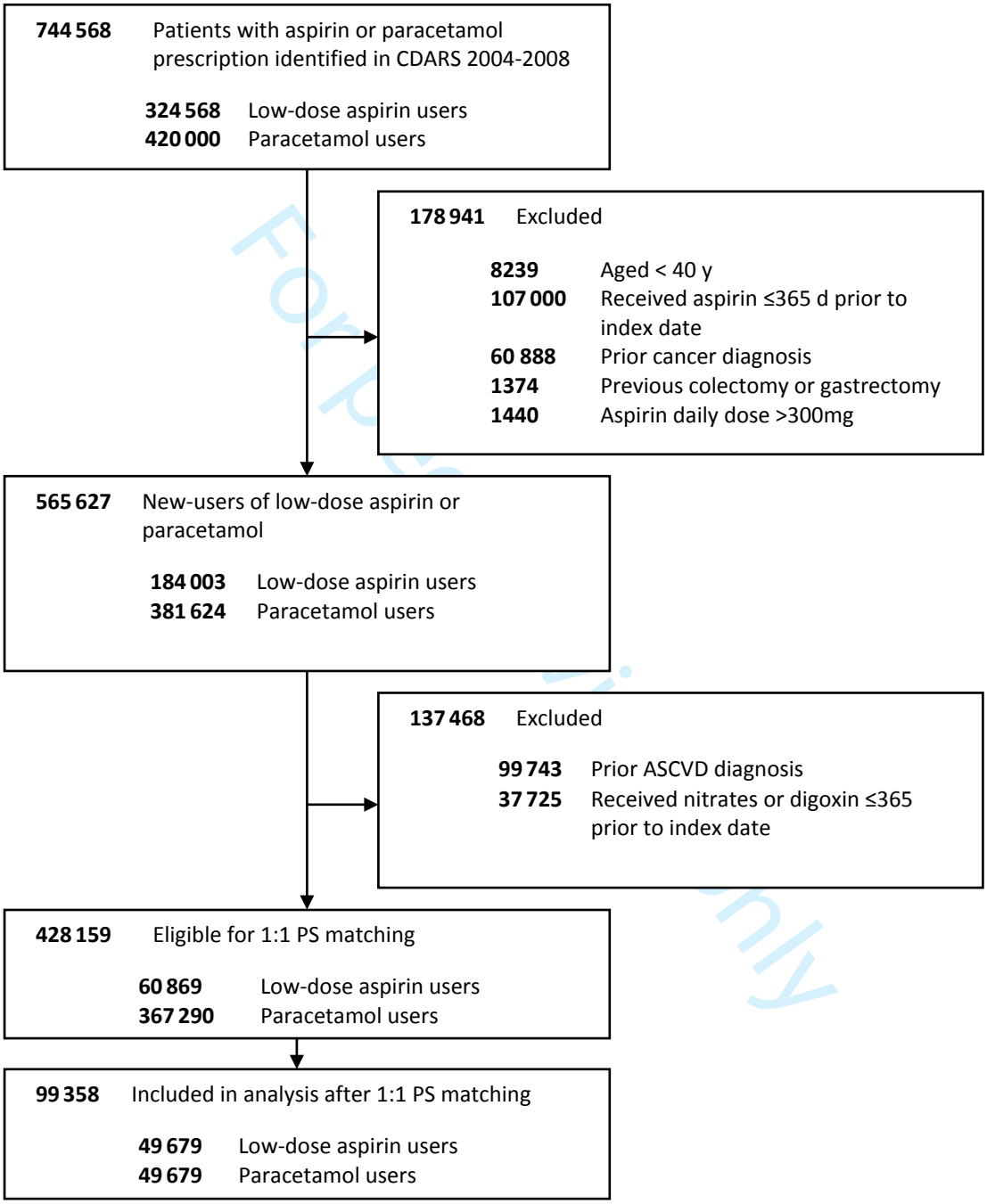
Table 3. Risk of Gastrointestinal Bleeding with Low-Dose Aspirin and Paracetamol After Propensity Score Matching

	Low-dose Aspirin			Paracetamol				
	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	HR (95% CI)	*P* Value
Overall	49 679	5498/431 246	12.27	49 679	5131/465 091	11.03	1.15 (1.11-1.20)	<.001
Female	24 031	2698/212 596	12.69	23 991	2510/229 792	10.92	1.16 (1.10-1.23)	<.001
Male	25 648	2800/218 650	12.81	25 688	2621/235 300	11.14	1.15 (1.09-1.21)	<.001
40-49 years old	4344	184/46 633	3.95	4002	190/45 506	4.18	0.94 (0.77-1.15)	.56
50-59 years old	9350	526/97 488	5.40	8416	476/93 363	5.10	1.05 (0.93-1.19)	.41
60-69 years old	11 489	1007/112 395	8.96	11 050	935/116 577	8.02	1.13 (1.03-1.23)	.008
70-79 years old	14 976	2153/122 814	17.53	15 326	1742/141 851	12.28	1.44 (1.35-1.53)	<.001
≥80 years old	9520	1628/51 916	31.36	10 885	1788/67 795	26.37	1.18 (1.11-1.27)	<.001
Diabetes Mellitus	6079	756/46 398	16.29	5975	752/49 701	15.13	1.07 (0.97-1.18)	.20
PPI/H2 blocker use	14 323	1682/113 597	14.81	13 898	1738/122 015	14.24	1.03 (0.96-1.10)	.46
Upper GIB	49 679	4964/431 246	11.51	49 679	4649/465 091	10.00	1.14 (1.09-1.18)	<.001
PPI/H2 blocker use	14 323	1513/113 597	13.32	13 898	1612/122 015	13.21	0.98 (0.91-1.05)	.54
Lower GIB	49 679	549/431 246	1.27	49 679	501/465 091	1.08	1.31 (1.16-1.48)	<.001
PPI/H2 blocker use	14 323	176/113 597	1.55	13 898	131/122 015	1.07	1.70 (1.35-2.14)	<.001

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitors.

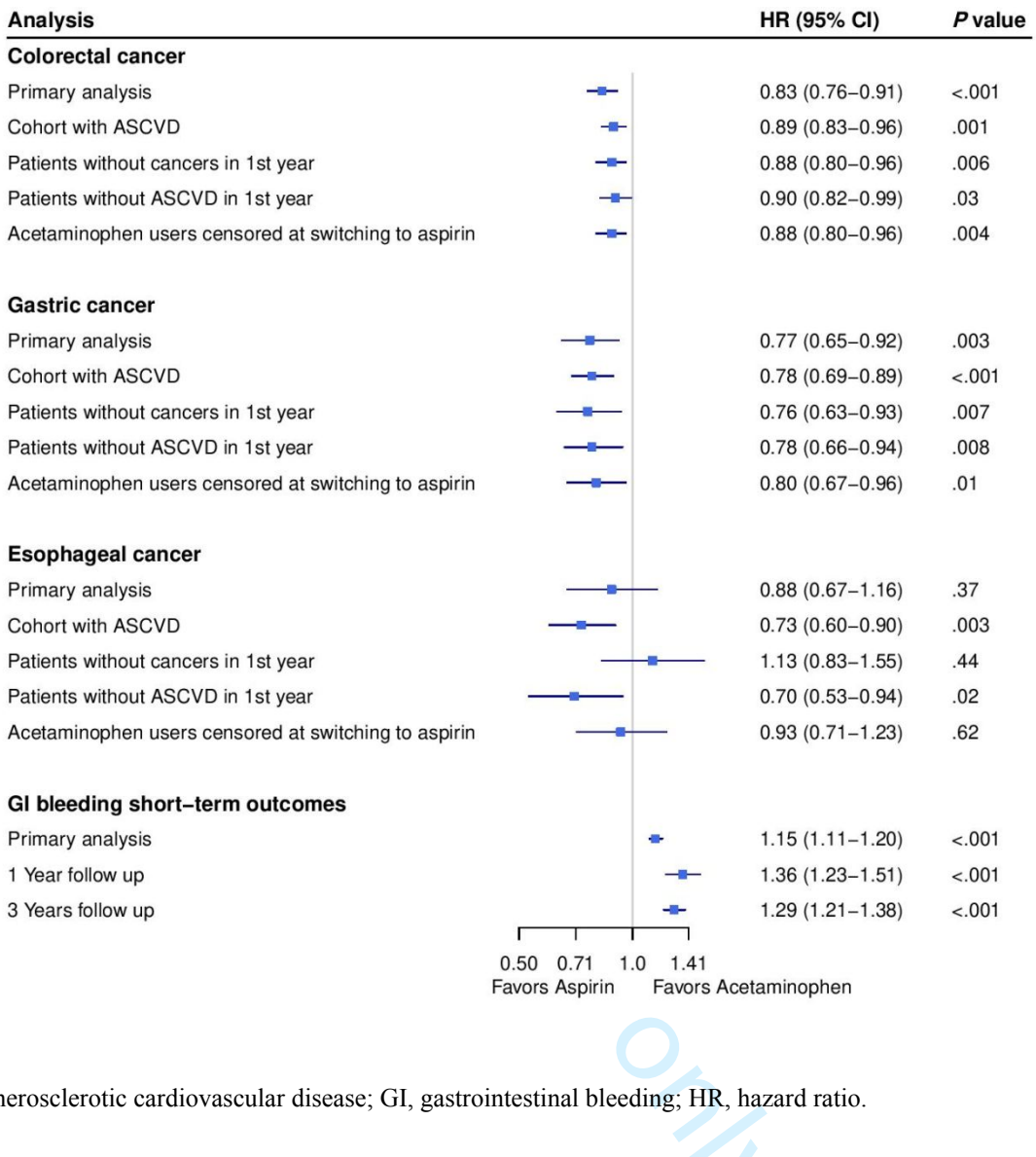
Figures

Figure 1. Selection of Low-dose Aspirin and Paracetamol Users for Analysis of Gastrointestinal Cancer and Gastrointestinal Bleeding Risk



ASCVD, atherosclerotic cardiovascular disease; CDARS indicates the Clinical Data Analysis and Reporting System (of the Hong Kong Hospital Authority); PS, propensity score.

Figure 2. Sensitivity Analyses



ASCVD, atherosclerotic cardiovascular disease; GI, gastrointestinal bleeding; HR, hazard ratio.

Supplementary Material

Supplementary Table 1. List of diagnosis and procedure codes used in the study

Supplementary Table 2. List of drug names and codes used in the study

Supplementary Table 3. Risk of Gastrointestinal Cancers and Gastrointestinal Bleeding with Low-Dose Aspirin and Acetaminophen Before Propensity Score Matching

Supplementary Figure 1. Propensity score plot before and after matching

Supplementary Table 1. List of diagnosis and procedure codes used in the study

Baseline characteristics	**ICD-9 codes**
Hypertension	401 – 405
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428
Arrhythmia and conduction disorders	426-427
Arterial disease	433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 440-445, 447, 557
Valve disorders	424
Cardiomyopathy	425
Diabetes mellitus	250
Hyperlipidemia	272.0-272.2, 272.4
Thyroid disorders	242-244
Major bleeding^	531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 578.0, 578.1, 578.9, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 569.86, 430, 431, 432.
COPD	490-492, 494, 496
Obesity	278
CKD	585
Chronic liver disease	570, 571
GERD	530.81
Irritable bowel syndrome	564.1
Peptic ulcer	533
Inflammatory bowel disease	556
Alcohol related disorders	265.2, 291.1, 291.2, 291.3, 291.5, 291.6, 291.7, 291.8, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.1, 571.2, 571.3, 980, V11.3
Schizophrenia and psychosis	295, 297, 298.3, 298.4, 298.8, 298.9
Bipolar disorder	296.0, 296.1, 296.4-296.7, 296.80, 296.81 296.89
Depression	296.2, 296.3, 296.82, 298.0, 300.4, 311
Outcomes	**ICD-9 codes**
Colorectal cancer	153, 154
Gastric cancer	151
Esophageal cancer	150
Gastrointestinal bleeding	531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 578.0, 578.1, 578.9, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 569.86

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease.

^ Major bleeding; bleeding that led to hospitalization in the last 365 days

Supplementary Table 2. List of drug names and codes used in the study

Baseline characteristics	Drug item code	Drug name
NSAIDs	CELE, DICL, SULI, PIRO, IBUP, NAPR, INDO02-03, ETOR, MELO	Celecoxib, Diclofenac, Sulindac, Piroxicam, Ibuprofen, Naproxen, Indomethacin, Etoricoxib, Meloxicam
Antiplatelet	ABCI, CLOP, DIPY, EPTI, TICA, PRAS	Dipyridamole, Clopidogrel, Prasugrel, Ticagrelor, Abciximab, Eptifibatide
Anticoagulants	APIX, DABI, EDOX, ARGA, WARF, HEPA03-04-05-11, TINZ, NADR, ENOX, EPOP	Apixaban, Dabigatran, Rivaroxaban, Edoxaban, Argatroban, Warfarin, Heparin, Tinzaparin, Nadroparin, Enoxaparin, Epoprostenol
Insulin	INSU	Biphasic Insulin Aspart, Biphasic Insulin Lispro, Insulin Human, Insulin Isophane Human, Insulin Neutral Human, Insulin Aspart Human, Insulin Degludec, Insulin Detemir, Insulin Glargine, Insulin Glulisine, Insulin Lispro Human
Oral hypoglycemic drugs	ACAR, ALOG, DAPA, DEXT01,18,22,28, 43,35,36, 70,71,72,75,76,78, 82,84,90,99, DIAZ07, DULA, EMPA, EXEN, GLIC, GLIP, GLIM, GLUC01,37, LINA, LIRA, LIXI, METF01,02, PIOG, SAXA, SITA, VILD	Acarbose, Alogliptin, Dapagliflozin, Dextrose, Diazoxide, Dulaglutide, Empagliflozin, Exenatide, Gliclazide, Glipizide, Glimepiride, Glucagon, Linagliptin, Liraglutide, Lixisenatide, Metformin, Pioglitazone, Saxagliptin, Sitagliptin, Vildagliptin
Lipid lowering drugs	ATOR01-02-03-04, FLUV-02-03-05, LOVA, PRAV-01-02, ROSU01-02, SIMV-01-02-04-05, ALIR, CHOL, EVOL, EZET, FENO, GEMF	Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin, Alirocumab, Cholestyramine, Evolocumab, Ezetimibe, Fenofibrate, Gemfibrozil
PPI or H2-blockers	ARIP01-02, ESOM01-02-03, LANS01-02-03-04, OMEP01-02-05-06-07, PANT-01-02-03, RABE-01-02, FAMO, RANI01,03,05,07	Aripiprazole, Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole, Famotidine, Ranitidine
Oral bisphosphonates	ALEN, CLOD, IBAN, PAMI, RISE, ZOLE	Alendronate, Clodronate, Ibandronic acid, Pamidronate, Risedronate, Zoledronic acid
Antipsychotics	AMIS, ARIP, CHLOR, CLOZ, FLUP, RISP, HALO03, HALO05, HALO06, HALO07, HALO08, HALO09, HALO11, HALO13, HALO14, LITH, LURA, OLAN, PALI, PERI01, PERI02, PIMO, QUET, SULP19, SULP20, TRIF, ZIPR, ZUCL	Amisulpride, Aripiprazole, Chlorpromazine, Clozapine, Flupenthixol, Risperidone, Fluphenazine, Haloperidol, Lithium, Lurasidone, Olanzapine, Paliperidone, Pericyazine, Pimozide, Quetiapine, Sulpiride, Trifluoperazine, Ziprasidone, Zuclopenthixol
Antidepressants	AMIT, AGOM, BUPR06, CLOM01, CLOM02, DEAN, DOTH, DOXE, FLUP01, FLUP02, FLUP03, FLUP04, FLUP11, PARO, IMIP, MIAN, VORT, MIRT, MOCL, NORT, TRAZ, TRIM05, TRIM06, TRIM13	Amitriptyline, Agomelatine, Bupropion, Clomipramine, Deanxit, Dothiepin, Doxepin, Flupenthixol, Paroxetine, Imipramine, Mianserin, Vortioxetine, Mirtazapine,

		Moclobemide, Nortriptyline, Trazodone, Trimipramine
Oral corticosteroids	BETA04, BETA06, BETA07, BETA08, BETA09, BETA13, BETA16, DEXA, FLUD, HYDR06, HYDR07, HYDR08, HYDR11, HYDR13, HYDR28, HYDR40, HYDR41, HYDR54, HYDR56, HYDR59, HYDR60, HYDR61, PRED01, PRED02, PRED06, PRED08, PRED09, PRED14, PRED15, PRED16, PRED17, PRED19, PRED21, PRED22, PRED23, PRED26, PRED27, METH29, METH30, METH36, METH37, METH66, METH67, METH71, TRIA02, TRIA03, TRIA04, TRIA09, TRIA13	Betamethasone, Dexamethasone, Fludrocortisone, Hydrocortisone, Prednisolone, Triamcinolone
Diuretics	AMIL, BUME, DYAZ, EPLE, FRUS, HYDR05, HYDR30, HYDR38, INDA, MANN, METO05, MODU, SPIR	Amiloride, Bumetanide, Dyazide, Eplerenone, Frusemide, Hydrochlorothiazide, Indapamide, Mannitol, Metolazone, Moduretic, Spironolactone
Anti-arrhythmic	AMIO, ATRO, DISO02, DISO03, DRON, FLEC, MEXI, PROC03, PROP01, QUIN02	Miodarone, Atropine, Disopyramide, Dronedarone, Flecainide, Mexiletine, Procainamide, Propafenone, Quinidine
Beta-blockers	ATEN, BISO, CARV, ESMO, LABE, METO06, METO07, METO08, METO09, METO10, METO11, METO13, METO15, METO16, NADO, PIND, PROP04, PROP05, PROP07, PROP08, PROP13, SOTA	Atenolol, Bisoprolol, Carvedilol, Esmolol, Labetalol, Metoprolol, Nadolol, Pindolol, Propranolol, Sotalol
ACE inhibitor or ARB	CAND, CAPT, ENAL, IRBE, LISI, LOSA, PERI17, PERI18, RAMI, TELM, VALS	Candesartan, Captopril, Enalapril, Irbesartan, Lisinopril, Losartan, Perindopril, Ramipril, Telmisartan, Valsartan
Other antihypertensive	CLON05, DOXA, HYDR01, HYDR02, HYDR03, ILOP, METH22, METH23, METH78, NITR06, PHEN16, PRAZ03, PRAZ04, PRAZ05, TERA	Lonidine, Doxazosin, Hydralazine, Iloprost, Methyldopa, Nitroprusside, Phenoxybenzamine, Phentolamine, Prazosin, Terazosin
CCB	AMLO, DILT, FELO, LERC, NIFE, NIMO, VERA	Amlodipine, Diltiazem, Felodipine, Lercanidipine, Nifedipine, Nimodipine, Verapamil
Peripheral vasodilators	CILO, IVAB, NAFT02, NAFT03, NICE, OXPE	Cilostazol, Ivabradine, Naftidrofuryl, Nicergoline, Oxpentifylline

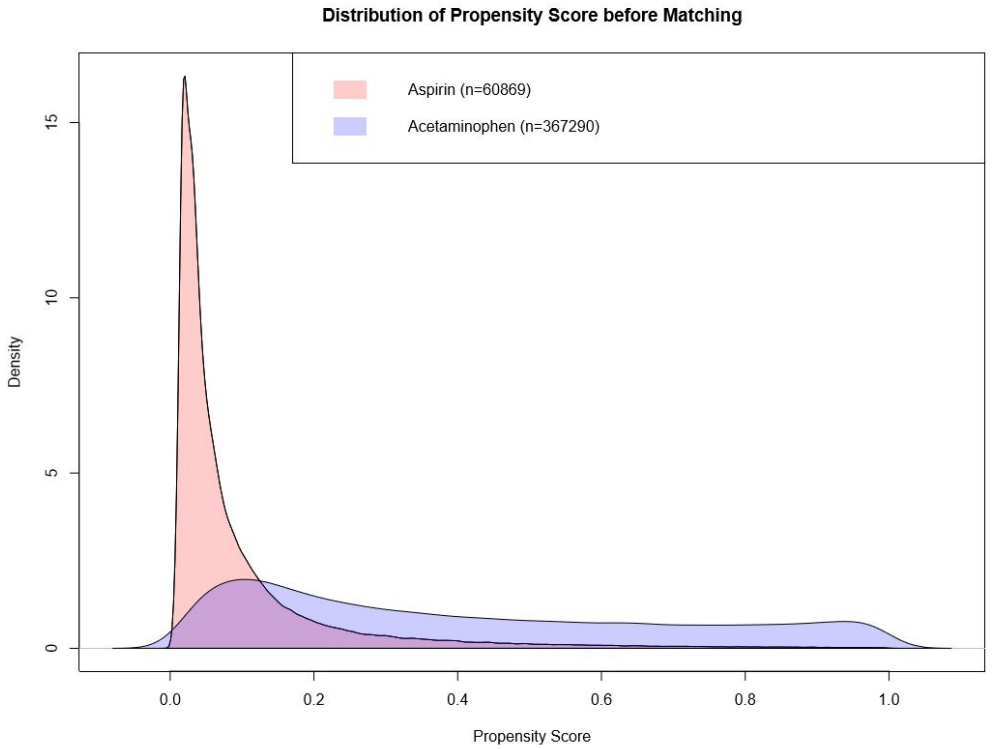
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitors.

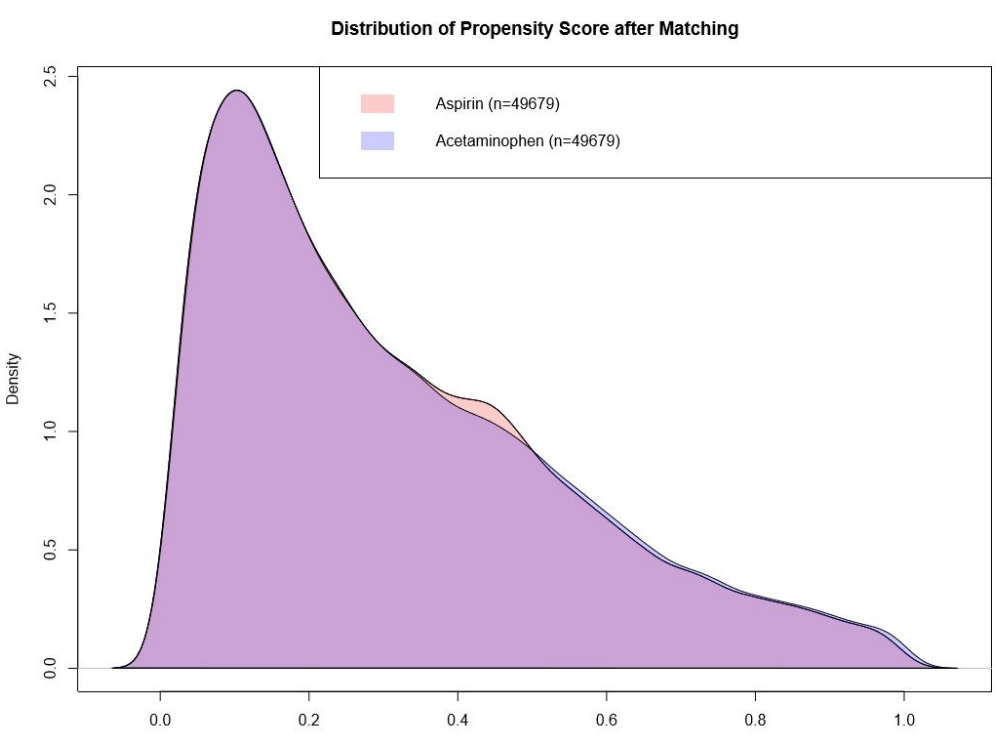
Supplementary Table 3. Risk of Gastrointestinal Cancers and Gastrointestinal Bleeding with Low-Dose Aspirin and Acetaminophen Before Propensity Score Matching

	Low-dose Aspirin			Acetaminophen			Low-dose Aspirin vs Acetaminophen	
	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	HR (95% CI)	*P* Value
Colorectal cancer	60 869	1085/498 618	2.18	367 290	4978/3 872 782	1.29	1.71 (1.60-1.83)	<.001
Gastric cancer	60 869	276/498 618	0.55	367 290	1223/3 872 782	0.32	1.74 (1.53-1.99)	<.001
Esophageal cancer	60 869	112/498 618	0.22	367 290	550/3 872 782	0.14	1.53 (1.25-1.88)	<.001
Gastrointestinal bleeding	60 869	7053/545 721	12.92	367 290	21 037/ 4 014 350	5.24	2.47 (2.40-2.54)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

Supplementary Figure 1. Propensity score plot before and after matching





STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

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Safety and effectiveness of low-dose aspirin for the prevention of gastrointestinal cancer in adults without atherosclerotic cardiovascular disease: a population based cohort study

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Title

Safety and effectiveness of low-dose aspirin for the prevention of gastrointestinal cancer in adults without atherosclerotic cardiovascular disease: a population based cohort study

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Abstract

Objective

To assess the association between low-dose aspirin and the incidence of colorectal cancer (CRC), gastric cancer (GC), esophageal cancer (EC), and gastrointestinal bleeding (GIB) in adults without established atherosclerotic cardiovascular disease.

Design

Cohort study with propensity score matching of new-users of aspirin to non-users.

Setting

Clinical Data Analysis and Reporting System database, Hong Kong.

Participants

Adults ≥ 40 years with a prescription start date of either low-dose aspirin (75-300 mg/daily) or paracetamol (non-aspirin users) between January 1, 2004 to December 31, 2008, without a history of atherosclerotic cardiovascular disease.

Main Outcome Measures

The primary outcome was the first diagnosis of gastrointestinal cancer (either CRC, GC, or EC), and the secondary outcome was GIB. Individuals were followed from index date of prescription until the earliest occurrence of an outcome of interest, an incident diagnosis of any type of cancer besides the outcome, death, or until December 31, 2017. A competing risk survival analysis was used, with death as the competing risk to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results

After matching, 49 679 aspirin and non-aspirin users were included. The median (IQR) follow-up was 10.0 (6.4) years. HRs for low-dose aspirin compared with non-aspirin users were 0.83 for CRC (95% CI 0.76 to 0.91), 0.77 for GC (95% CI 0.65 to 0.92), and 0.88 for EC (0.67 to 1.16). Low-dose aspirin was associated with an increased risk of GIB (HR 1.15, 95% CI 1.11 to 1.20), except for patients taking proton pump inhibitors or histamine H2-receptor antagonists (HR 1.03, 95% CI 0.96-1.10).

Conclusion

In this cohort study of Chinese adults, low-dose aspirin was associated with a reduced risk of CRC and GC, and an increased risk of GIB. Among patients taking gastroprotective agents at baseline, however, the association with GIB was attenuated.

Keywords

Aspirin; gastrointestinal neoplasms; gastrointestinal hemorrhage, primary prevention, Chinese population; cohort study

Article summary

Strengths and limitations of this study

- This is the first study to evaluate the association of low-dose aspirin with gastrointestinal cancer (i.e., colorectal cancer, gastric cancer, and esophageal cancer) and gastrointestinal bleeding among Chinese adults without atherosclerotic cardiovascular disease.
- This population-based cohort study has a large sample size, long duration of follow-up, and used electronic health records from an integrated health care system that captures aspirin prescriptions and cancer outcomes.
- Complete information, however, was not available for alcohol consumption, smoking status, and body mass index, which could be associated with the outcomes of interest.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death with approximately 1.8 million new cases and 826,000 deaths worldwide in 2018.[1] The incidence of colorectal cancer is estimated to rise to 2.2 million people by 2030, with 1.1 million colorectal cancer associated deaths.[2] Apart from CRC, gastric cancer (GC) and esophageal cancer (EC) also pose a public health threat worldwide, with approximately 1 million and 600,000 new cases in 2018 respectively.[3]

Given the significant burden of gastrointestinal (GI) cancers, pharmacological intervention may play an important role in reducing their risk. The use of low-dose aspirin to prevent GI cancers is controversial with different studies showing inconsistent results.[4-7] Evidence from randomized clinical trials (RCTs) is the "gold standard" for assessing the efficacy of treatments. Although no trial has specifically assessed low-dose aspirin for the prevention of GI cancers, a patient-level meta-analysis of aspirin trials suggests an association with a reduced risk of CRC after long-term follow-up.[8] In addition to trial evidence, pooling of observational studies also demonstrate an association with a reduced risk of GI cancers.[9] Given the accumulating evidence of benefit for low-dose aspirin, the US Preventative Services Task Force (USPSTF) currently recommends initiation of low-dose aspirin for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) and CRC, only for patients aged between 50 to 69 years with ≥10% 10-year risk of ASCVD who are not at an increased risk of bleeding.[10]

The risk-benefit ratio for low-dose aspirin, however, may differ by ethnicity. A recent study showed that the protective effects of aspirin on CRC varied among ethnicities with the strongest association of benefit observed among Caucasians.[11] Furthermore, low-dose aspirin modestly increases the risk of gastrointestinal bleeding (GIB),[12] which might outweigh the GI

cancer prevention benefits. The risk of GIB is especially a concern among the Chinese population as they are suspected to have a higher risk of bleeding.[13 14] Considering the possible variation in the effects of low-dose aspirin on GI cancer, as well as in the risk of GIB, further studies conducted in Asian populations are warranted.

This study aimed to investigate the association of low-dose aspirin with the risk of CRC, GC, EC, and GIB among adults ≥40 years without pre-existing ASCVD in Hong Kong.

Methods

Data source

We used the Clinical Data Analysis and Reporting System (CDARS), which contains electronic health records for patients receiving care from the Hospital Authority (HA), a statutory body that manages all public hospitals and their clinics in Hong Kong. All Hong Kong residents have access to public healthcare services and around 80% of hospitalizations in Hong Kong are in HA hospitals. CDARS stores clinical records from 1993 and has been used to conduct pharmacoepidemiologic studies, with high accuracy in coding the study outcomes in previous validation studies (positive predictive value: GI bleed, 100%; GI cancer, 100%).[15-17]

Study design and patient selection

This was a population-wide retrospective cohort study. Patients ≥40 years with a prescription start date of either low-dose aspirin (75-300 mg/daily) or paracetamol between January 1, 2004 and December 31, 2008 were identified in CDARS. The date of the first low-dose aspirin or paracetamol prescription was considered the index date. Since CDARS captures both prescribing and dispensing with the Hospital Authority system, the prescription start date matched the dispensing date for 99% of the prescription records in our data set. To include new users of low-dose aspirin, patients with a prescription of aspirin one year prior to the index date were excluded. Patients diagnosed with any type of cancer, those who underwent a colectomy or gastrectomy, or diagnosed with ASCVD defined as ischemic heart disease, cerebrovascular disease, or peripheral artery disease before the index date were excluded. Nitrates and digoxin were used as proxies to indicate a history of ASCVD, hence, any patient with a nitrate or digoxin prescription in the year prior to the index date were also excluded **(Supplementary Table 1 & 2)**.

Patients who received paracetamol (non-aspirin users) were identified as the reference group for risk comparison. Paracetamol, was used to identify patients who have had contact with the healthcare system during the same calendar time period as the low-dose aspirin patients. Importantly, paracetamol is not indicated for any associated comorbidities and has no known association with any type of cancer. An intention-to-treat approach was adopted, where patients allocated to the low-dose aspirin group on the index date will remain in the low-dose aspirin group, and similarly for the non-aspirin group.

Outcomes

The primary outcomes of this study were the development of either CRC, GC, or EC. The follow-up period started from the date of first prescription of either low-dose aspirin or paracetamol (i.e. index date) and was censored at the incident diagnosis of any cancer, death, or end of study period (December 31, 2017). Patients diagnosed with CRC, GC, and EC were identified using International classification of diseases 9th revision (ICD-9) codes **(Supplementary Table 1)**. The secondary outcome was GIB that led to a hospital visit (diagnosis code for an in-patient, out-patient or accident and emergency room visit). The follow-up period started from the index date and was censored at diagnosis of the outcome, death or end of study period.

Study variables

Potential confounders included patient demographics (age, sex), comorbidities (diabetes mellitus, hyperlipidemia, hypertension, obesity, alcohol related disorders, congestive heart failure, arrhythmia and conduction disorders, arterial disease, valve disorders, cardiomyopathy, chronic kidney disease, hepatic failure, chronic obstructive pulmonary disease [COPD], thyroid disorders, schizophrenia, depression, bipolar disorder, peptic ulcer, gastrointestinal reflux, irritable bowel syndrome, inflammatory bowel syndrome, and bleeds

that led to hospitalization within one year prior to index date), and concomitant medication use one year prior to index date (nonsteroidal anti-inflammatory drugs [NSAIDs], antiplatelets, anticoagulants, oral hypoglycemic agents, insulin, diuretics, antihypertensive agents, anti-arrhythmic, calcium channel blockers, beta-blockers, angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor, peripheral vasodilators, lipid-lowering drugs, oral bisphosphonates, oral corticosteroids, proton pump inhibitors [PPI]/histamine-2 receptor blockers (H2-blockers), antidepressants, and antipsychotics).

Although evidence indicates a potential chemoprotective role of estrogens on the risk of certain cancers a prescription of estrogens (either as oral contraceptive or menopausal hormone) was not included as a study variable due to the small number of patients with an estrogen therapy (233 [0.47%] and 244 [0.49%] in low-dose aspirin and paracetamol users respectively).

Statistical analysis

Baseline characteristics of low-dose aspirin users and non-aspirin users were presented as frequencies (percentages) for categorical variables and as mean (±SD) for continuous variables. To reduce confounding arising from baseline differences between low-dose aspirin and non-aspirin users, propensity score (PS) matching was performed. Aforementioned confounders were included in estimating the PS value. Patients using low-dose aspirin and paracetamol were matched at a 1:1 ratio using a nearest neighbor algorithm with a caliper of 0.01. Standardized mean difference (SMD) <0.1 between treatment groups was considered acceptable/negligible.

The ratio of incidence per 1000-person years of CRC, GC, and EC among low-dose aspirin users and non-aspirin users was reported. The association of CRC, GC, and EC with the use of low-dose aspirin was estimated using competing risk Cox regression with death as the

competing risk, and hazard ratio (HR) with 95% confidence interval (CI) was reported. The association of GIB with the use of low-dose aspirin was estimated using a Cox regression and HR with 95% CI was reported. The number needed to treat (NNT) and number needed to harm (NNH) was estimated using the equation; 1/absolute risk reduction and 1/absolute risk increase respectively.

Subgroup analysis was performed to investigate the risk of GI cancer and GIB in low-dose aspirin and non-aspirin users with different age groups (40-49 years old, 50-59 years old, 60-69 years old, 70-79 years old, and ≥80 years old). Since the use of gastroprotective agents (PPI/H2-blockers) could reduce the risk of GIB in patients on antithrombotic agents,[18] we assessed the association of GI cancer and GIB with the use of low-dose aspirin in patients on gastroprotective agents. As people with diabetes are at higher risk of developing cancer[19], we also evaluated the association of low-dose aspirin with GI cancer and GIB among this population. Lastly, the association between low-dose aspirin and GIB has been shown to be different depending on the location of the GIB. Therefore, we stratified the GIB outcome to upper GIB (UGIB) and lower GIB (LGIB).

Sensitivity analyses were conducted by excluding patients with cancer diagnosis during the first year of follow-up since the cancer could have developed before the start of follow-up. Patients with an ASCVD diagnosis during the first year of follow-up were removed to ensure all patients included have no pre-existing ASCVD. Non-aspirin users with a low-dose aspirin prescription during follow-up were censored at the first aspirin prescription. Lastly, the effectiveness of low-dose aspirin for GI cancer prevention was evaluated in patients taking low-dose aspirin for secondary ASCVD prevention; patients taking low-dose aspirin for primary and secondary ASCVD were included.

R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. The analyses were conducted by JS and cross-checked independently by JZ for quality assurance.

Patient and public involvement

There was no patient and public involvement.

Results

Baseline characteristics

We identified 324 568 aspirin and 420 000 non-aspirin users between January 1, 2004 and December 31, 2008. Following exclusion criteria, 428 159 patients were eligible for the PS matching **(Figure 1).** A total of 99 358 individuals (49 679 low-dose aspirin users and 49 679 matched non-aspirin users) were successfully matched (**Supplementary Figure 1)**. After matching, all baseline characteristics had SMD < 0.1 and were well balanced. The mean (standard deviation [SD]) age for the cohort was 68.6 (12.6) years, and 48 022 (48.4%) were women **(Table 1).** The median (interquartile range [IQR]) follow-up for the cohort was 10.0 (6.4) years for the GI cancer outcome (9.8 [6.3] years low-dose aspirin users and 10.4 [6.3] years non-aspirin users), and 10.2 (5.9) years for the GIB outcome (9.9 [6.1] years low-dose aspirin users and 10.6 [5.7] years non-aspirin users)**.** The most common dose of aspirin was 80 mg daily (72.2%).

Risk of Gastrointestinal Cancer

In the propensity score-matched sample, 1954 of 99 358 participants developed CRC (876 low-dose aspirin users [1.7%] and 1078 non-aspirin users [2.2%]), 515 GC (222 [0.4%] and 293 [0.6%]), and 206 EC (96 [0.2%] and 110 [0.2%], respectively; **Table 2**). The results for the unmatched cohort are presented in **Supplementary Table 3**. The number of patients who died due to CRC, GC and EC were 247 (28.2%), 99 (44.6%) and 51 (53.1%) in low-dose aspirin users respectively, and 360 (33.4%), 151 (51.5%) and 55 (50.0%) in non-aspirin users respectively. NNT is 250 and 500 for CRC and GC respectively, and the NNH is 125 for GIB.

The results from the competing risk survival analysis showed that low-dose aspirin use was significantly associated with a lower risk of CRC and GC compared to non-aspirin users (CRC: HR, 0.83 [95% CI, 0.76-0.91]; GC: 0.77 [0.65-0.92]), but not with EC (HR, 0.88 [95% CI, 0.67-1.16]; **Table 2**). The association with lower risk was statistically significant for females (CRC: HR, 0.79 [95% CI, 0.68-0.90]; GC: 0.73 [0.54-0.98]) and males (CRC: HR, 0.86 [95% CI, 0.76-96]; GC: 0.79 [0.64-0.98]). The use of low-dose aspirin was significantly associated with a lower risk of CRC in patients aged between 70 to 79 years old (HR, 0.82 [95% CI, 0.71-0.94]) and among patients with diabetes (HR, 0.73 [95% CI, 0.57-0.94]), with a lower risk of GC among patients 80 years and older (HR, 0.60 [95% CI, 0.43-0.84]; **Table 2**).

There was no significant association between low-dose aspirin and esophageal cancer in any of the subgroup analysis (**Table 2**). The test for the interaction effect of low-dose aspirin and gastroprotective agents was not significant when assessing the association between low-dose aspirin and gastrointestinal cancer, with and without gastroprotective agents (*P* value for interaction, >0.5).

Risk of Gastrointestinal Bleeding

In the propensity score-matched sample, 10 629 of 99 358 participants had a GIB event (5498 low-dose aspirin users [11.1%] and 5131 non-aspirin users [10.3%]; **Table 3**). Among patients with a GIB diagnosis the number of patients who died due to a GIB was 88 (1.6%) in low-dose aspirin users and 83 (1.6%) in non-aspirin users. Compared to non-aspirin users, low-dose aspirin was significantly associated with an increased risk of GIB (HR, 1.15 [95% CI, 1.11-1.20]). The association with higher risk was statistically significant for females (HR, 1.16 [95% CI, 1.10-1.23]) and males (HR, 1.15 [95% CI, 1.09-1.21]), in addition to patients

aged 60 to 69 (HR, 1.13 [95% CI, 1.03-1.23]), 70 to 79 (HR, 1.44 [95% CI, 1.35-1.53]), and 80 years and older (HR, 1.18 [95% CI, 1.11-1.27].

Low-dose aspirin was not significantly associated with an increased risk of GIB in patients aged 40 to 49 (HR, 0.94 [95% CI, 0.77-1.15]) and 50 to 59 (HR, 1.05 [95% CI, 0.93-1.19]) as well as in patients with diabetes (HR, 1.07 [95% CI, 0.97-1.18]) and those taking gastroprotective agents (HR, 1.03 [95% CI, 0.96-1.10]; **Table 3**). The test for subgroup difference indicated significant difference between the association with and without gastroprotective agents (*P* value for interaction <0.001) (**Supplementary Table 4)**.

Low-dose aspirin was significantly associated with an increased risk of UGIB (HR, 1.14 [95% CI, 1.09-1.18]) and LGIB (HR, 1.31 [95% CI, 1.16-1.48]). The association with higher risk remained for LGIB among patients taking gastroprotective agents (HR, 1.70 [95% CI, 1.35-2.14]), however, low-dose aspirin was not associated with an increased risk of UGIB in those taking gastroprotective agents (HR, 0.98 [95% CI, 0.91-1.05]).

Sensitivity analysis

After removing patients with a cancer diagnosis during the first year of follow-up, the association remained similar for CRC (HR, 0.88 [95% CI, 0.80-0.96]), GC (HR, 0.76 [95% CI, 0.63-0.93]), and EC (HR, 1.13 [95% CI, 0.83-1.55]; **Figure 2).** The association with lower risk also remained after removing patients with a diagnosis of ASCVD during the first year of follow-up for CRC (HR, 0.90 [95% CI, 0.82-0.99]), GC (HR, 0.78 [95% CI, 0.66-0.94]), and EC (HR, 0.70 [95% CI, 0.53-0.94]). Lastly, the lower risk remained when censoring non-aspirin users at the first aspirin prescription during follow-up in CRC (HR, 0.88 [95% CI, 0.80-0.96]), and GC (HR, 0.80 [95% CI, 0.67-0.96]) but not EC (HR, 0.93 [95% CI, 0.71-1.23]). After combining all patients taking low-dose aspirin for either primary or secondary prevention of ASCVD, they had a lower risk of CRC (HR, 0.89 [95% CI, 0.83-

0.96]), GC (HR, 0.78 [95% CI, 0.69-0.89]), as well as EC (HR, 0.73 [95% CI, 0.60-0.90]) compared to non-aspirin users.

Discussion

In Chinese adults without pre-existing ASCVD, our results suggest that the use of low-dose aspirin was associated with a lower risk of CRC and GC, but not EC, as compared to non-aspirin users during a median follow-up of 10 years. However, low-dose aspirin was associated with an increased risk of GIB. Nevertheless, a subgroup analysis showed that the use of low-dose aspirin was not associated with an increased risk of GIB among patients younger than 60 years old and those taking PPIs or H2-blockers.

Our findings are consistent with a meta-analysis of patient follow-up (maximum duration 20 years) from five RCTs which showed that aspirin was associated with a reduced risk of colorectal cancer (HR 0.76; 95% CI = 0.60-0.96).[8] In addition to RCTs, observational studies have also examined the association of low-dose aspirin with GI cancer.[20-27] Although studies have consistently shown a beneficial effect of using low-dose aspirin, findings from both RCTs and observational studies have largely been limited to Caucasians.[20 22-24 27] An earlier study in Hong Kong evaluated the risk of GIB and benefit of CRC reduction from the use of low-dose aspirin and found that low-dose aspirin lowered the risk of CRC but at the cost of a higher risk of GIB. The authors acknowledged that the results could be inaccurate due to confounding by indication since no comorbidities were used to adjust for baseline differences between aspirin and non-aspirin users.[28] Our present study adjusted for observed baseline differences between aspirin and non-aspirin users by using PS matching. Moreover, most studies include patients taking low-dose aspirin for both primary and secondary prevention of ASCVD. However, the clinical implications for the primary prevention cohort is greater as initiating low-dose aspirin is no longer standard practice for this population.

A study in the United Kingdom has evaluated the protective effect of low-dose aspirin on CRC in a cohort with no pre-existing CVD.[4] However, the risk of GIB was not investigated.

Nevertheless, the association of low-dose aspirin with a reduced risk of GI cancer was consistent with our findings. Furthermore, our findings are also consistent with our recent 13-year cohort study conducted in Hong Kong (N=74 161) which found that regular aspirin use was associated with a decrease in gastric cancer risk following *Helicobacter pylori* eradication.[16] Daily use, prolonged use, and use of higher doses of aspirin after *Helicobacter pylori* eradication was associated with significant reduction in the risk of gastric cancer.[16]

The role of low-dose aspirin for the prevention of GI cancer is equivocal and questions remain, particularly for patients without a history of ASCVD. Some RCTs have reported no reductions in GI cancer incidence and mortality with the use of low-dose aspirin. [5 7] The Aspirin in Reducing Events in the Elderly (ASPREE) trial reported a higher mortality rate in patients taking low-dose aspirin compared to placebo. A secondary analysis showed cancer as the major contributor to the higher mortality rate (HR: 1.13; 1.10-1.56), with a subgroup analysis for GI cancer which detected no differences between groups (CRC: RR, 0.97 [0.77-1.24]).[6] Patients in the ASPREE trial were ≥70 years old, hence the benefits of low-dose aspirin for GI cancer prevention may be limited since most of the benefits of low-dose aspirin are apparent in studies of younger adults with longer duration of use.[29] Notably, Asians comprised only 1% of the trial population in ASPREE. Therefore, findings from ASPREE may be more applicable to healthy Caucasian adults.

Potential clinical implications

The finding that low-dose aspirin use was associated with a lower risk of CRC and GC is of particular clinical importance, especially among patients with no pre-existing ASCVD, since the decision to initiate low-dose aspirin is less well defined. GI cancers are major contributors to mortality worldwide with no proven preventative treatment. Aspirin is affordable, easily accessible and has a recognized pharmacological profile which could be a means to

improving the burden of disease. Additionally, the risk of GIB associated with low-dose aspirin is of particular interest in the Chinese population, which has a different bleeding profile compared to Caucasians.[14] Lastly, our study showed that for every 1000 patients taking low-dose aspirin, 6 GI cancer cases could be prevented, although it could cause 8 GIBs. However, the percentage of patients with GI cancer outcome who died was 30% to 50% compared to 1.6% for GIB. In addition, the percentage of fatal GIB (1.6%) is similar in both the low-dose aspirin and non-aspirin group. This indicates that the use of low-dose aspirin does not contribute to an increase in the risk of fatal GIB. Further, this is consistent with a meta-analysis published in 2016 which evaluated fatal GIB attributable to low-dose aspirin.[30] This information along with the knowledge that patients under 60 years or those taking gastroprotective agents are not at higher risk of GIB could inform clinical decisions to initiate low-dose aspirin in Chinese adults without ASCVD who highly value preventing CRC and GC.

Strengths and limitations

To our knowledge, this is the first study to evaluate the association of low-dose aspirin with GI cancer and GIB among patients without ASCVD. The findings are likely generalizable to other urban Chinese populations with similar risks of GI cancer as the population of Hong Kong. We used PS matched cohort study to emulate a target randomized trial since the feasibility of an RCT is low due to the large sample size and long follow-up that is required to evaluate cancer outcomes. Furthermore, while low-dose aspirin is a non-prescription medication in Hong Kong, its cost is heavily subsidized ($15 HKD ~ $2 USD for 4-month supply) through the public healthcare system. Thus, misclassification of exposure to low-dose aspirin is likely minimal.[14]

This study has several limitations. Similar to some electronic health record databases, information such as body mass index, smoking status, and alcohol consumption are not routinely recorded in CDARS. However, other confounders were used as proxy to account for these risk factors (COPD and alcohol related disorders). A general limitation of cohort studies is the residual and the unmeasured confounding bias which cannot be excluded. Finally, subgroup analyses by age, diabetes mellitus, and use of gastroprotective agents should be interpreted as hypothesis generating results since the low number of events upon stratification resulted in limited statistical power.

Our findings support a potential role for low-dose aspirin therapy for the prevention of colorectal and gastric cancer, but not esophageal cancer, in Chinese adults ≥40 years. Further research, such as a pragmatic RCT, is needed to confirm the observed association in a patient population that would be expected to derive the most benefit, and least harm, from taking low-dose aspirin.

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Data sharing

No additional data are available.

Author contributions

Dr. Chan and Ms. Shami had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Shami, Zhao, Chan, Wong.

Acquisition, analysis, or interpretation of data: Shami, Zhao, Pathadka, Wan, Chan, Wong.

Drafting of the manuscript: Shami

Critical revision of the manuscript for important intellectual content: Shami, Zhao, Pathadka, Wan, Blais, Cheung, Leung, Wong, Chan..

Statistical analysis: Shami, Zhao, Wan.

Administrative, technical, or material support: Vora, Soriano-Gabarro, Wong, Chan.

Supervision: Chan, Wong.

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Conflict of interest

Dr Chan has received honorarium from the Hospital Authority and research funding from The Hong Kong Research Grants Council, The Research Fund Secretariat of the Food and Health Bureau, Narcotics Division of the Security Bureau of HKSAR, Hong Kong; National Natural Science Fund of China, China; Wellcome Trust, United Kingdom; Bristol-Myers Squibb, Pfizer, and Takeda, for work unrelated to this study. Professor Wong has received research funding outside the submitted work from the Hong Kong Research Grants Council and the Hong Kong Health and Medical Research Fund, National Institute for Health Research in the UK, European Commission, Amgen, Bayer, Bristol-Myers Squibb, GSK, and Janssen. Mr. Vora and Ms. Soriano-Gabarro are employees of Bayer AG. The remaining authors have no conflict of interest to declare.

Transparency declaration

Ms. Jessica Shami affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Jessica Shami

Dissemination declaration

Dissemination to study participants and or patient organizations is not possible.

License statement

relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Ethics statement

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number: UW 18-033). Informed patient consent was not required as the data used in this study were anonymized.

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Tables

Table 1. Baseline Characteristics of Low-Dose Aspirin and Paracetamol Users[a]

Characteristics	Before Propensity Score Matching			After Propensity Score Matching		
	Low-dose Aspirin (n=60 869)	Paracetamol (n=367 290)	Standardized Difference [b]	Low-dose Aspirin (n=49 679)	Paracetamol (n=49 679)	Standardized Difference [b]
Age, mean (SD), y	69.1 (12.5)	57.6 (12.8)	0.912	68.0 (12.5)	69.1 (12.7)	0.09
Female	29 010 (47.7)	211 841 (57.7)	0.202	24 031 (48.4)	23 991 (48.3)	0.002
Aspirin dose						
≤100 mg	52 125 (85.6)	-	-	42 756 (86.1)	-	-
101 mg – 200 mg	7396 (12.2)	-	-	5909 (11.9)	-	-
200 mg – 300 mg	1348 (2.2)	-	-	1014 (2.0)	-	-
Medical conditions						
Hypertension	12 679 (20.8)	18 469 (5.0)	0.485	8651 (17.4)	8626 (17.4)	0.001
Congestive heart failure	3676 (6.0)	1568 (0.4)	0.321	1734 (3.5)	1289 (2.6)	0.05
Arrhythmia and conduction disorders	8397 (13.8)	3563 (1.0)	0.506	3915 (7.9)	2900 (5.8)	0.08
Arterial disease	601 (1.0)	578 (0.2)	0.110	378 (0.8)	321 (0.6)	0.01
Valve disorders	436 (0.7)	579 (0.2)	0.085	266 (0.5)	254 (0.5)	0.003
Cardiomyopathy	329 (0.5)	149 (0.0)	0.093	165 (0.3)	114 (0.2)	0.02
Diabetes mellitus	9079 (14.9)	12 148 (3.3)	0.412	6079 (12.2)	5975 (12.0)	0.006
Hyperlipidemia	2130 (3.5)	2662 (0.7)	0.194	1400 (2.8)	1325 (2.7)	0.009
Thyroid disorders	1189 (2.0)	4644 (1.3)	0.055	851 (1.7)	837 (1.7)	0.002
Major bleeding	408 (0.7)	1269 (0.3)	0.046	316 (0.6)	343 (0.7)	0.007
COPD	2868 (4.7)	6214 (1.7)	0.172	2062 (4.2)	2109 (4.2)	0.005
Obesity	214 (0.4)	358 (0.1)	0.054	139 (0.3)	144 (0.3)	0.002
CKD	1359 (2.2)	1343 (0.4)	0.165	801 (1.6)	737 (1.5)	0.01
Chronic liver disease	544 (0.9)	1953 (0.5)	0.043	437 (0.9)	462 (0.9)	0.005
GERD	150 (0.2)	410 (0.1)	0.032	105 (0.2)	115 (0.2)	0.004

Irritable bowel syndrome	45 (0.1)	293 (0.1)	0.002	37 (0.1)	41 (0.1)	0.003
Peptic ulcer	244 (0.4)	952 (0.3)	0.025	193 (0.4)	186 (0.4)	0.002
Inflammatory bowel disease	11 (0.0)	106 (0.0)	0.007	10 (0.0)	8 (0.0)	0.003
Alcoholism	1166 (1.9)	3005 (0.8)	0.095	826 (1.7)	836 (1.7)	0.002
Schizophrenia	1125 (1.8)	5699 (1.6)	0.023	900 (1.8)	916 (1.8)	0.002
Bipolar disorder	95 (0.2)	706 (0.2)	0.009	87 (0.2)	98 (0.2)	0.005
Depression	1158 (1.9)	6291 (1.7)	0.014	943 (1.9)	942 (1.9)	<0.001
Medications						
Diuretics	14 350 (23.6)	28 961 (7.9)	0.441	10 042 (20.2)	10 136 (20.4)	0.005
ACE inhibitor or ARB	16 819 (27.6)	20 267 (5.5)	0.623	11 195 (22.5)	11 003 (22.1)	0.009
Other antihypertensives	8785 (14.4)	18 471 (5.0)	0.321	6384 (12.9)	6676 (13.4)	0.02
CCB	22 514 (37.0)	45 062 (12.3)	0.599	16 622 (33.5)	17 637 (35.5)	0.04
Anti-arrhythmic	1562 (2.6)	1335 (0.4)	0.184	760 (1.5)	537 (1.1)	0.04
Beta-blockers	21 756 (35.7)	42 667 (11.6)	0.592	15 777 (31.8)	16 466 (33.1)	0.03
Peripheral vasodilators	741 (1.2)	598 (0.2)	0.128	435 (0.9)	373 (0.8)	0.01
Oral hypoglycemic	14 789 (24.3)	25 443 (6.9)	0.493	10 799 (21.7)	11 260 (22.7)	0.02
Insulin	3321 (5.5)	2686 (0.7)	0.275	1972 (4.0)	1790 (3.6)	0.02
Lipid lowering drugs	10 680 (17.5)	10 362 (2.8)	0.502	7019 (14.1)	6835 (13.8)	0.01
PPI or H2-blockers	21 143 (34.7)	39 028 (10.6)	0.601	14 323 (28.8)	13 898 (28.0)	0.02
NSAID	8324 (13.7)	62 026 (16.9)	0.089	7137 (14.4)	7503 (15.1)	0.02
Oral bisphosphonates	245 (0.4)	455 (0.1)	0.054	182 (0.4)	186 (0.4)	0.001
Oral corticosteroids	7561 (12.4)	30 915 (8.4)	0.131	5913 (11.9)	6136 (12.4)	0.01
Anticoagulants	2537 (4.2)	1359 (0.4)	0.257	1278 (2.6)	962 (1.9)	0.04
Antiplatelet	1408 (2.3)	328 (0.1)	0.205	532 (1.1)	316 (0.6)	0.05
Antipsychotics	2172 (3.6)	7718 (2.1)	0.088	1664 (3.3)	1708 (3.4)	0.005
Antidepressants	2583 (4.2)	10 947 (3.0)	0.068	2063 (4.2)	2110 (4.2)	0.005

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitors.

[a] Values are expressed as frequency (%) unless otherwise specified. [b] Standardized difference indicates difference in mean or proportion of covariates in the low-dose aspirin group vs the paracetamol group divided by the pooled standard deviation.

Table 2. Risk of Gastrointestinal Cancers with Low-Dose Aspirin and Paracetamol After Propensity Score Matching

	Low-dose Aspirin			Paracetamol				
	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	HR (95% CI)	*P* Value
Colorectal cancer	49 679	876/428 554	2.04	49 679	1078/457 195	2.36	0.83 (0.76-0.91)	<.001
Female	24 031	356/211 588	1.68	23 991	463/226 257	2.05	0.79 (0.68-0.90)	<.001
Male	25 648	520/216 966	2.40	25 688	615/230 938	2.66	0.86 (0.76-0.96)	.01
40-49 years old	4344	15/45 459	0.33	4002	26/44 565	0.58	0.57 (0.30-1.06)	.08
50-59 years old	9350	90/95 162	0.95	8416	105/91 025	1.15	0.84 (0.63-1.11)	.20
60-69 years old	11 489	224/110 070	2.04	11 050	250/112 834	2.22	0.89 (0.74-1.07)	.19
70-79 years old	14 976	352/123 565	2.85	15 326	446/139 167	3.20	0.82 (0.71-0.94)	.004
≥80 years old	9520	195/54 298	3.59	10 885	251/69 604	3.61	0.89 (0.74-1.07)	.23
Diabetes Mellitus	6079	108/46 923	2.30	5975	147/49 238	2.99	0.73 (0.57-0.94)	.01
PPI/H2 blocker use	14 323	224/112 848	1.98	13 898	262/120 357	2.18	0.85 (0.71-1.02)	.07
Gastric cancer	49 679	222/428 554	0.52	49 679	293/457 195	0.64	0.77 (0.65-0.92)	.003
Female	24 031	73/211 591	0.35	23 991	103/226 259	0.46	0.73 (0.54-0.98)	.04
Male	25 648	149/216 969	0.69	25 688	190/230 940	0.82	0.79 (0.64-0.98)	.03
40-49 years old	4344	5/45 459	0.11	4002	8/44 565	0.18	0.58 (0.19-1.77)	.34
50-59 years old	9350	31/95 162	0.33	8416	21/91 025	0.23	1.40 (0.80-2.45)	.24
60-69 years old	11 489	41/110 070	0.37	11 050	52/112 834	0.46	0.78 (0.51-1.17)	.22
70-79 years old	14 976	93/123 565	0.75	15 326	113/139 167	0.81	0.85 (0.65-1.12)	.26
≥80 years old	9520	52/54 298	0.96	10 885	99/69 604	1.42	0.60 (0.43-0.84)	.003
Diabetes Mellitus	6079	28/46 923	0.60	5975	40/49 238	0.81	0.69 (0.43-1.13)	.14
PPI/H2 blocker use	14 323	65/112 848	0.58	13 898	82/120 357	0.68	0.77 (0.56-1.07)	.12
Esophageal cancer	49 679	96/428 554	0.22	49 679	110/457 195	0.24	0.88 (0.67-1.16)	.37
Female	24 031	23/211 591	0.11	23 991	29/226 259	0.13	0.80 (0.46-1.39)	.43

Male	25 648	73/216 969	0.34	25 688	81/230 940	0.35	0.91 (0.66-1.25)	.55
40-49 years old	4344	2/45 459	0.04	4002	1/44 565	0.02	2.05 (0.22-19.5)	.53
50-59 years old	9350	11/95 162	0.12	8416	11/91 025	0.12	0.95 (0.41-2.19)	.90
60-69 years old	11 489	30/110 070	0.27	11 050	25/112 834	0.22	1.19 (0.70-2.02)	.53
70-79 years old	14 976	35/123 565	0.28	15 326	39/139 167	0.28	0.92 (0.58-1.45)	.72
≥80 years old	9520	18/54 298	0.33	10 885	34/69 604	0.49	0.61 (0.34-1.07)	.08
Diabetes Mellitus	6079	13/46 923	0.28	5975	19/49 238	0.39	0.67 (0.33-1.36)	.27
PPI/H2 blocker use	14 323	28/112 848	0.25	13 898	29/120 357	0.24	0.94 (0.56-1.58)	.82

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitors.

Table 3. Risk of Gastrointestinal Bleeding with Low-Dose Aspirin and Paracetamol After Propensity Score Matching

	Low-dose Aspirin			Paracetamol				
	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	HR (95% CI)	*P* Value
Overall	49 679	5498/431 246	12.27	49 679	5131/465 091	11.03	1.15 (1.11-1.20)	<.001
Female	24 031	2698/212 596	12.69	23 991	2510/229 792	10.92	1.16 (1.10-1.23)	<.001
Male	25 648	2800/218 650	12.81	25 688	2621/235 300	11.14	1.15 (1.09-1.21)	<.001
40-49 years old	4344	184/46 633	3.95	4002	190/45 506	4.18	0.94 (0.77-1.15)	.56
50-59 years old	9350	526/97 488	5.40	8416	476/93 363	5.10	1.05 (0.93-1.19)	.41
60-69 years old	11 489	1007/112 395	8.96	11 050	935/116 577	8.02	1.13 (1.03-1.23)	.008
70-79 years old	14 976	2153/122 814	17.53	15 326	1742/141 851	12.28	1.44 (1.35-1.53)	<.001
≥80 years old	9520	1628/51 916	31.36	10 885	1788/67 795	26.37	1.18 (1.11-1.27)	<.001
Diabetes Mellitus	6079	756/46 398	16.29	5975	752/49 701	15.13	1.07 (0.97-1.18)	.20
PPI/H2 blocker use	14 323	1682/113 597	14.81	13 898	1738/122 015	14.24	1.03 (0.96-1.10)	.46
Upper GIB	49 679	4964/431 246	11.51	49 679	4649/465 091	10.00	1.14 (1.09-1.18)	<.001
PPI/H2 blocker use	14 323	1513/113 597	13.32	13 898	1612/122 015	13.21	0.98 (0.91-1.05)	.54
Lower GIB	49 679	549/431 246	1.27	49 679	501/465 091	1.08	1.31 (1.16-1.48)	<.001
PPI/H2 blocker use	14 323	176/113 597	1.55	13 898	131/122 015	1.07	1.70 (1.35-2.14)	<.001

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitors.

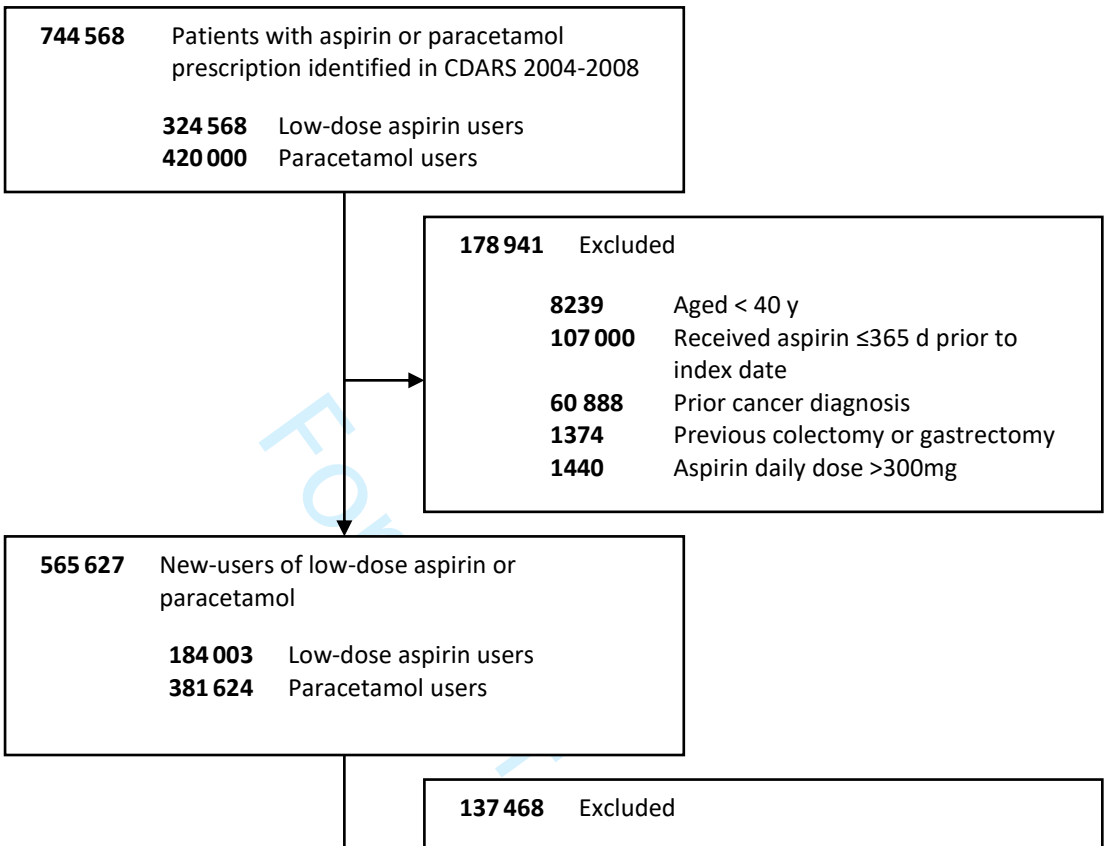
Figure legends

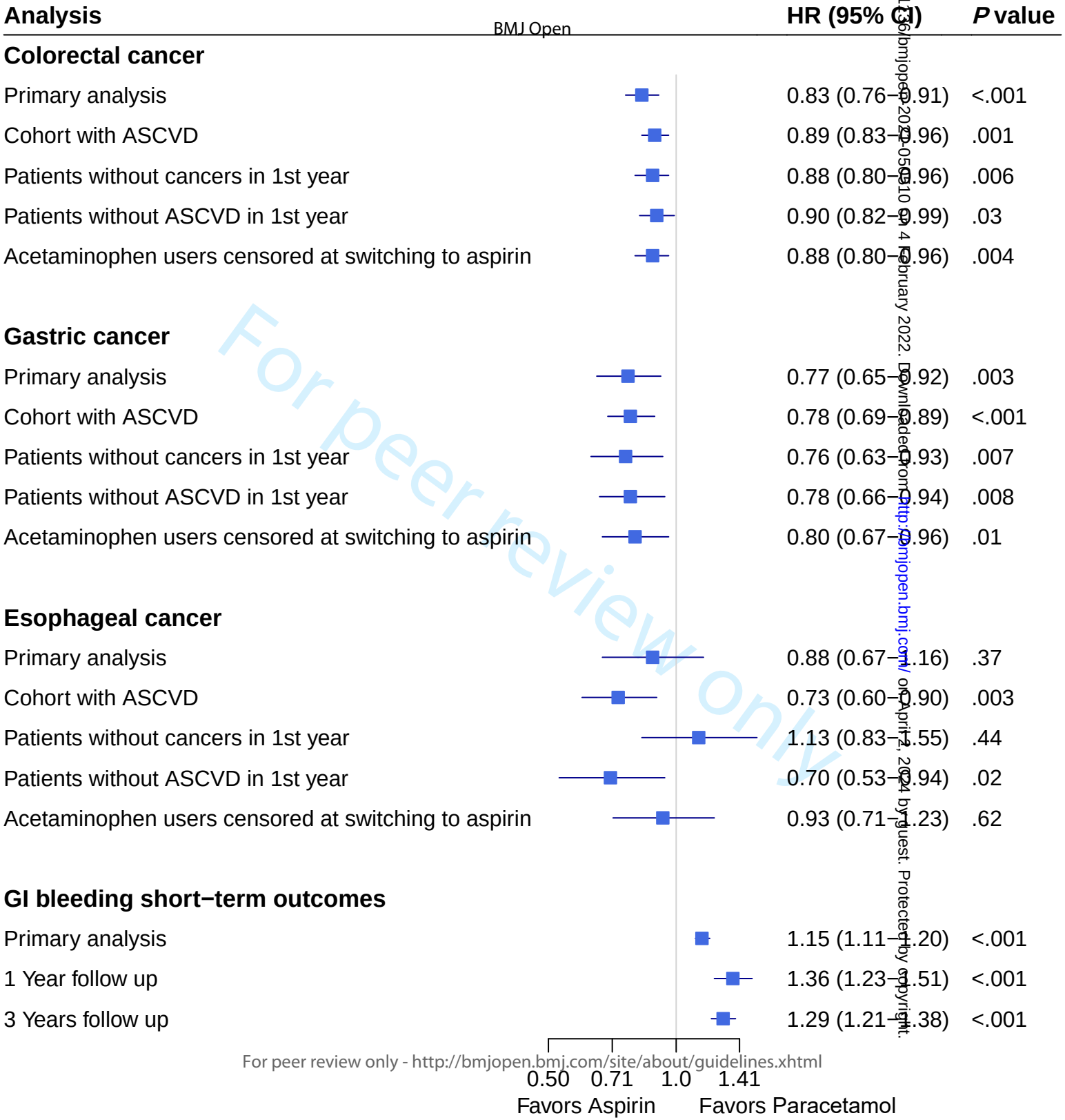
Figure 1. Flow chart of users in the cohort study assessing the risk of gastrointestinal cancer and gastrointestinal bleeding

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CDARS, Clinical Data Analysis and Reporting System (of the Hong Kong Hospital Authority); PS, propensity score.

Figure 2. Forest plot of the results of the primary and sensitivity analyses

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; GI, gastrointestinal bleeding; HR, hazard ratio.





Supplementary Material

Supplementary Table 1. List of diagnosis and procedure codes used in the study

Supplementary Table 2. List of drug names and codes used in the study

Supplementary Table 3. Risk of gastrointestinal cancers and gastrointestinal bleeding with low-dose aspirin and paracetamol before propensity score matching

Supplementary Table 4. Number of patients with a prescription of proton pump inhibitors and H2 receptor antagonists during baseline

Supplementary Figure 1. Propensity score plot before and after matching

Supplementary Table 1. List of diagnosis and procedure codes used in the study

Baseline characteristics	**ICD-9 codes**
Hypertension	401 – 405
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428
Arrhythmia and conduction disorders	426-427
Arterial disease	433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 440-445, 447, 557
Valve disorders	424
Cardiomyopathy	425
Diabetes mellitus	250
Hyperlipidemia	272.0-272.2, 272.4
Thyroid disorders	242-244
Major bleeding^	531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 578.0, 578.1, 578.9, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 569.86, 430, 431, 432.
COPD	490-492, 494, 496
Obesity	278
CKD	585
Chronic liver disease	570, 571
GERD	530.81
Irritable bowel syndrome	564.1
Peptic ulcer	533
Inflammatory bowel disease	556
Alcohol related disorders	265.2, 291.1, 291.2, 291.3, 291.5, 291.6, 291.7, 291.8, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.1, 571.2, 571.3, 980, V11.3
Schizophrenia and psychosis	295, 297, 298.3, 298.4, 298.8, 298.9
Bipolar disorder	296.0, 296.1, 296.4-296.7, 296.80, 296.81 296.89
Depression	296.2, 296.3, 296.82, 298.0, 300.4, 311
Outcomes	**ICD-9 codes**
Colorectal cancer	153, 154
Gastric cancer	151
Esophageal cancer	150
Gastrointestinal bleeding	531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 578.0, 578.1, 578.9, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 569.86

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease.

^ Major bleeding; bleeding that led to hospitalization in the last 365 days

Supplementary Table 2. List of drug names and codes used in the study

Baseline characteristics	Drug item code	Drug name
NSAIDs	CELE, DICL, SULI, PIRO, IBUP, NAPR, INDO02-03, ETOR, MELO	Celecoxib, Diclofenac, Sulindac, Piroxicam, Ibuprofen, Naproxen, Indomethacin, Etoricoxib, Meloxicam
Antiplatelet	ABCI, CLOP, DIPY, EPTI, TICA, PRAS	Dipyridamole, Clopidogrel, Prasugrel, Ticagrelor, Abciximab, Eptifibatide
Anticoagulants	APIX, DABI, EDOX, ARGA, WARF, HEPA03-04-05-11, TINZ, NADR, ENOX, EPOP	Apixaban, Dabigatran, Rivaroxaban, Edoxaban, Argatroban, Warfarin, Heparin, Tinzaparin, Nadroparin, Enoxaparin, Epoprostenol
Insulin	INSU	Biphasic Insulin Aspart, Biphasic Insulin Lispro, Insulin Human, Insulin Isophane Human, Insulin Neutral Human, Insulin Aspart Human, Insulin Degludec, Insulin Detemir, Insulin Glargine, Insulin Glulisine, Insulin Lispro Human
Oral hypoglycemic drugs	ACAR, ALOG, DAPA, DEXT01,18,22,28, 43,35,36, 70,71,72,75,76,78, 82,84,90,99, DIAZ07, DULA, EMPA, EXEN, GLIC, GLIP, GLIM, GLUC01,37, LINA, LIRA, LIXI, METF01,02, PIOG, SAXA, SITA, VILD	Acarbose, Alogliptin, Dapagliflozin, Dextrose, Diazoxide, Dulaglutide, Empagliflozin, Exenatide, Gliclazide, Glipizide, Glimepiride, Glucagon, Linagliptin, Liraglutide, Lixisenatide, Metformin, Pioglitazone, Saxagliptin, Sitagliptin, Vildagliptin
Lipid lowering drugs	ATOR01-02-03-04, FLUV-02-03-05, LOVA, PRAV-01-02, ROSU01-02, SIMV-01-02-04-05, ALIR, CHOL, EVOL, EZET, FENO, GEMF	Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin, Alirocumab, Cholestyramine, Evolocumab, Ezetimibe, Fenofibrate, Gemfibrozil
PPI or H2-blockers	ARIP01-02, ESOM01-02-03, LANS01-02-03-04, OMEP01-02-05-06-07, PANT-01-02-03, RABE-01-02, FAMO, RANI01,03,05,07	Aripiprazole, Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole, Famotidine, Ranitidine
Oral bisphosphonates	ALEN, CLOD, IBAN, PAMI, RISE, ZOLE	Alendronate, Clodronate, Ibandronic acid, Pamidronate, Risedronate, Zoledronic acid
Antipsychotics	AMIS, ARIP, CHLOR, CLOZ, FLUP, RISP, HALO03, HALO05, HALO06, HALO07, HALO08, HALO09, HALO11, HALO13, HALO14, LITH, LURA, OLAN, PALI, PERI01, PERI02, PIMO, QUET, SULP19, SULP20, TRIF, ZIPR, ZUCL	Amisulpride, Aripiprazole, Chlorpromazine, Clozapine, Flupenthixol, Risperidone, Fluphenazine, Haloperidol, Lithium, Lurasidone, Olanzapine, Paliperidone, Pericyazine, Pimozide, Quetiapine, Sulpiride, Trifluoperazine, Ziprasidone, Zuclopenthixol
Antidepressants	AMIT, AGOM, BUPR06, CLOM01, CLOM02, DEAN, DOTH, DOXE, FLUP01, FLUP02, FLUP03, FLUP04, FLUP11, PARO, IMIP, MIAN, VORT, MIRT, MOCL, NORT, TRAZ, TRIM05, TRIM06, TRIM13	Amitriptyline, Agomelatine, Bupropion, Clomipramine, Deanxit, Dothiepin, Doxepin, Flupenthixol, Paroxetine, Imipramine, Mianserin, Vortioxetine, Mirtazapine,

		Moclobemide, Nortriptyline, Trazodone, Trimipramine
Oral corticosteroids	BETA04, BETA06, BETA07, BETA08, BETA09, BETA13, BETA16, DEXA, FLUD, HYDR06, HYDR07, HYDR08, HYDR11, HYDR13, HYDR28, HYDR40, HYDR41, HYDR54, HYDR56, HYDR59, HYDR60, HYDR61, PRED01, PRED02, PRED06, PRED08, PRED09, PRED14, PRED15, PRED16, PRED17, PRED19, PRED21, PRED22, PRED23, PRED26, PRED27, METH29, METH30, METH36, METH37, METH66, METH67, METH71, TRIA02, TRIA03, TRIA04, TRIA09, TRIA13	Betamethasone, Dexamethasone, Fludrocortisone, Hydrocortisone, Prednisolone, Triamcinolone
Diuretics	AMIL, BUME, DYAZ, EPLE, FRUS, HYDR05, HYDR30, HYDR38, INDA, MANN, METO05, MODU, SPIR	Amiloride, Bumetanide, Dyazide, Eplerenone, Frusemide, Hydrochlorothiazide, Indapamide, Mannitol, Metolazone, Moduretic, Spironolactone
Anti-arrhythmic	AMIO, ATRO, DISO02, DISO03, DRON, FLEC, MEXI, PROC03, PROP01, QUIN02	Miodarone, Atropine, Disopyramide, Dronedarone, Flecainide, Mexiletine, Procainamide, Propafenone, Quinidine
Beta-blockers	ATEN, BISO, CARV, ESMO, LABE, METO06, METO07, METO08, METO09, METO10, METO11, METO13, METO15, METO16, NADO, PIND, PROP04, PROP05, PROP07, PROP08, PROP13, SOTA	Atenolol, Bisoprolol, Carvedilol, Esmolol, Labetalol, Metoprolol, Nadolol, Pindolol, Propranolol, Sotalol
ACE inhibitor or ARB	CAND, CAPT, ENAL, IRBE, LISI, LOSA, PERI17, PERI18, RAMI, TELM, VALS	Candesartan, Captopril, Enalapril, Irbesartan, Lisinopril, Losartan, Perindopril, Ramipril, Telmisartan, Valsartan
Other antihypertensive	CLON05, DOXA, HYDR01, HYDR02, HYDR03, ILOP, METH22, METH23, METH78, NITR06, PHEN16, PRAZ03, PRAZ04, PRAZ05, TERA	Lonidine, Doxazosin, Hydralazine, Iloprost, Methyldopa, Nitroprusside, Phenoxybenzamine, Phentolamine, Prazosin, Terazosin
CCB	AMLO, DILT, FELO, LERC, NIFE, NIMO, VERA	Amlodipine, Diltiazem, Felodipine, Lercanidipine, Nifedipine, Nimodipine, Verapamil
Peripheral vasodilators	CILO, IVAB, NAFT02, NAFT03, NICE, OXPE	Cilostazol, Ivabradine, Naftidrofuryl, Nicergoline, Oxpentifylline

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitors.

Supplementary Table 3. Risk of gastrointestinal cancers and gastrointestinal bleeding with low-dose aspirin and paracetamol before propensity score matching

	Low-dose Aspirin			Paracetamol			Low-dose Aspirin vs Paracetamol	
	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	HR (95% CI)	*P* Value
Colorectal cancer	60 869	1085/498 618	2.18	367 290	4978/3 872 782	1.28	1.71 (1.60-1.83)	<.001
Gastric cancer	60 869	276/498 618	0.55	367 290	1223/3 872 782	0.32	1.74 (1.53-1.99)	<.001
Esophageal cancer	60 869	112/498 618	0.22	367 290	550/3 872 782	0.14	1.53 (1.25-1.88)	<.001
Gastrointestinal bleeding	60 869	7053/545 721	12.92	367 290	21 037/ 4 014 350	5.24	2.47 (2.40-2.54)	<.001

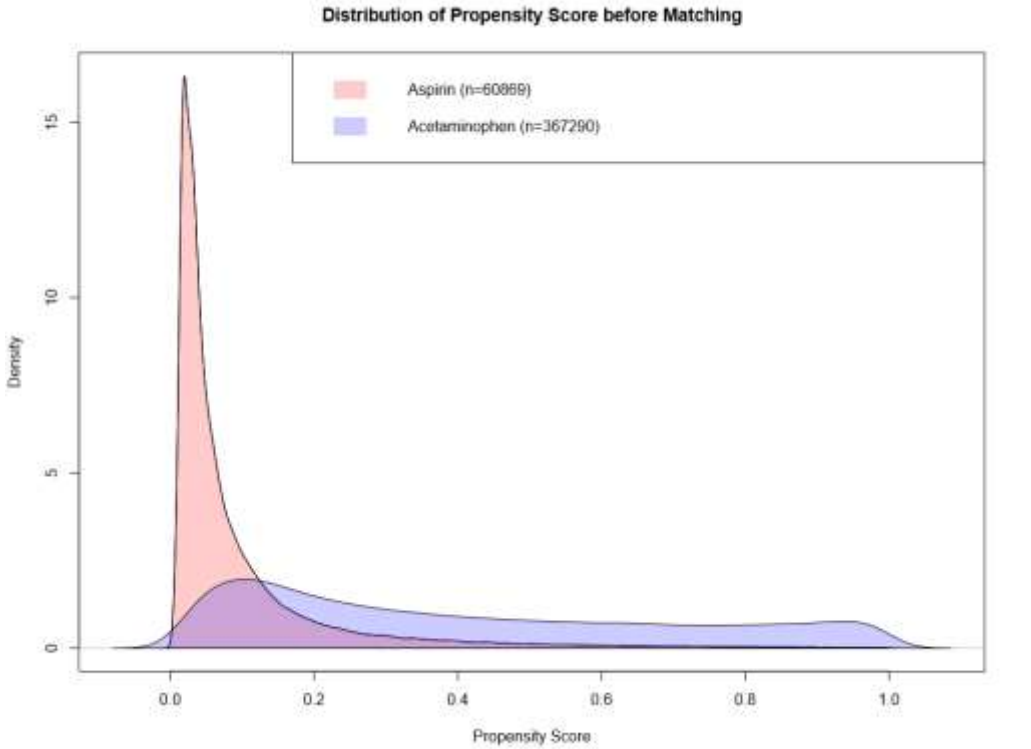
Abbreviations: CI, confidence interval; HR, hazard ratio.

Supplementary Table 4. Number of patients with a prescription of proton pump inhibitors and H2 receptor antagonists during baseline

	Low-dose aspirin users	***Paracetamol users***
Prescribed PPI or H2 blockers (%)	*14323 (28.8)*	*13,898 (28.0)*
PPI	3945 (27.5)	4317 (31.1)
Esomeprazole	1125 (28.5)	1342 (31.1)
20mg	774 (68.8)	667 (49.7)
40mg	351 (31.2)	675 (50.3)
Lansoprazole	409 (10.4)	502 (11.6)
15mg	21 (5.1)	38 (7.6)
30mg	388 (94.4)	464 (92.4)
Omeprazole	65 (1.6)	333 (7.7)
20mg	4 (5.7)	145 (43.5)
40mg	61 (94.3)	188 (56.5)
Pantoprazole	1081 (27.4)	1295 (30.0)
20mg	288 (26.6)	190 (14.7)
40mg	793 (73.4)	1105 (85.3)
Rabeprazole	1265 (32.1)	845 (19.6)
10mg	161 (12.7)	125 (14.8)
20mg	1104 (87.3)	720 (85.2)
H2 blockers	13230 (92.4)	13552 (97.5)
Famotidine	13118 (99.2)	12886 (95.1)
20mg	11491 (87.6)	11804 (91.6)
40mg	1627 (12.4)	1082 (8.4)
Ranitidine	112 (0.8)	666 (4.9)
150mg	110 (98.3)	661 (99.2)
400mg	2 (1.7)	5 (0.8)

Abbreviations: PPI, proton pump inhibitors; H2 blockers, Histamine-2 receptor antagonists.

Supplementary Figure 1. Propensity score plot before and after matching



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
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Safety and effectiveness of low-dose aspirin for the prevention of gastrointestinal cancer in adults without atherosclerotic cardiovascular disease: a population based cohort study

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Title

Safety and effectiveness of low-dose aspirin for the prevention of gastrointestinal cancer in adults without atherosclerotic cardiovascular disease: a population based cohort study

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Abstract

Objective

To assess the association between low-dose aspirin and the incidence of colorectal cancer (CRC), gastric cancer (GC), esophageal cancer (EC), and gastrointestinal bleeding (GIB) in adults without established atherosclerotic cardiovascular disease.

Design

Cohort study with propensity score matching of new-users of aspirin to non-users.

Setting

Clinical Data Analysis and Reporting System database, Hong Kong.

Participants

Adults ≥ 40 years with a prescription start date of either low-dose aspirin (75-300 mg/daily) or paracetamol (non-aspirin users) between January 1, 2004 to December 31, 2008, without a history of atherosclerotic cardiovascular disease.

Main Outcome Measures

The primary outcome was the first diagnosis of gastrointestinal cancer (either CRC, GC, or EC) and the secondary outcome was GIB. Individuals were followed from index date of prescription until the earliest occurrence of an outcome of interest, an incident diagnosis of any type of cancer besides the outcome, death, or until December 31, 2017. A competing risk survival analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) with death as the competing risk.

Results

After matching, 49 679 aspirin and non-aspirin users were included. The median (IQR) follow-up was 10.0 (6.4) years. HRs for low-dose aspirin compared with non-aspirin users were 0.83 for CRC (95% CI 0.76 to 0.91), 0.77 for GC (95% CI 0.65 to 0.92), and 0.88 for EC (0.67 to 1.16). Patients prescribed low-dose aspirin had an increased risk of GIB (HR 1.15, 95% CI 1.11 to 1.20), except for patients prescribed proton pump inhibitors or histamine H2-receptor antagonists (HR 1.03, 95% CI 0.96-1.10).

Conclusion

In this cohort study of Chinese adults, patients prescribed low-dose aspirin had reduced risks of CRC and GC and an increased risk of GIB. Among the subgroup of patients prescribed gastroprotective agents at baseline, however, the association with GIB was attenuated.

Keywords

Aspirin; gastrointestinal neoplasms; gastrointestinal hemorrhage, primary prevention, Chinese population; cohort study

Article summary

Strengths and limitations of this study

- This is the first study to evaluate the association of low-dose aspirin with gastrointestinal cancer (i.e., colorectal cancer, gastric cancer, and esophageal cancer) and gastrointestinal bleeding among Chinese adults without atherosclerotic cardiovascular disease.
- This population-based cohort study has a large sample size, long duration of follow-up, and used electronic health records from an integrated health care system that captures aspirin prescriptions and cancer outcomes.
- Complete information, however, was not available for alcohol consumption, smoking status, and body mass index, which could be associated with the outcomes of interest.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death with approximately 1.8 million new cases and 826,000 deaths worldwide in 2018.[1] The incidence of colorectal cancer is estimated to rise to 2.2 million people by 2030, with 1.1 million colorectal cancer associated deaths.[2] Apart from CRC, gastric cancer (GC) and esophageal cancer (EC) also pose a public health threat worldwide, with approximately 1 million and 600,000 new cases in 2018 respectively.[3]

Given the significant burden of gastrointestinal (GI) cancers, pharmacological intervention may play an important role in reducing their risk. The use of low-dose aspirin to prevent GI cancers is controversial with different studies showing inconsistent results.[4-7] Evidence from randomized clinical trials (RCTs) is the "gold standard" for assessing the efficacy of treatments. Although no trial has specifically assessed low-dose aspirin for the prevention of GI cancers, a patient-level meta-analysis of aspirin trials suggests an association with a reduced risk of CRC after long-term follow-up.[8] In addition to trial evidence, pooling of observational studies also demonstrate an association with a reduced risk of GI cancers.[9] Given the accumulating evidence of benefit for low-dose aspirin, the US Preventative Services Task Force (USPSTF) currently recommends initiation of low-dose aspirin for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) and CRC, only for patients aged between 50 to 69 years with ≥10% 10-year risk of ASCVD who are not at an increased risk of bleeding.[10]

The risk-benefit ratio for low-dose aspirin, however, may differ by ethnicity. A recent study showed that the protective effects of aspirin on CRC varied among ethnicities with the strongest association of benefit observed among Caucasians.[11] Furthermore, low-dose aspirin modestly increases the risk of gastrointestinal bleeding (GIB),[12] which might outweigh the GI

cancer prevention benefits. The risk of GIB is especially a concern among the Chinese population as they are suspected to have a higher risk of bleeding.[13 14] Considering the possible variation in the effects of low-dose aspirin on GI cancer, as well as in the risk of GIB, further studies conducted in Asian populations are warranted.

This study aimed to investigate the association of low-dose aspirin with the risk of CRC, GC, EC, and GIB among adults ≥40 years without pre-existing ASCVD in Hong Kong.

Methods

Data source

We used the Clinical Data Analysis and Reporting System (CDARS), which contains electronic health records for patients receiving care from the Hospital Authority (HA), a statutory body that manages all public hospitals and their clinics in Hong Kong. All Hong Kong residents have access to public healthcare services and around 80% of hospitalizations in Hong Kong are in HA hospitals. CDARS stores clinical records from 1993 and has been used to conduct pharmacoepidemiologic studies, with high accuracy in coding the study outcomes in previous validation studies (positive predictive value: GI bleed, 100%; GI cancer, 100%).[15-17]

Study design and patient selection

This was a population-wide retrospective cohort study. Patients ≥40 years who were either prescribed low-dose aspirin (75-300 mg/daily) or paracetamol by a doctor within the HA, and with a prescription start date between January 1, 2004 and December 31, 2008 were identified in CDARS. The date of the first low-dose aspirin or paracetamol prescription was considered the index date. Since CDARS captures both prescribing and dispensing with the Hospital Authority system, the prescription start date matched the dispensing date for 99% of the prescription records in our data set. To include new users of low-dose aspirin, patients with a prescription of aspirin one year prior to the index date were excluded. Patients diagnosed with any type of cancer, those who underwent a colectomy or gastrectomy, or diagnosed with ASCVD defined as ischemic heart disease, cerebrovascular disease, or peripheral artery disease before the index date were excluded. Nitrates and digoxin were used as proxies to indicate a history of ASCVD, hence, any patient with a nitrate or digoxin

prescription in the year prior to the index date were also excluded **(Supplementary Table 1 & 2)**.

Patients who received paracetamol (non-aspirin users) were identified as the reference group for risk comparison. Paracetamol, was used to identify patients who have had contact with the healthcare system during the same calendar time period as the low-dose aspirin patients. Importantly, paracetamol is not indicated for any associated comorbidities and has no known association with any type of cancer. An intention-to-treat approach was adopted, where patients allocated to the low-dose aspirin group on the index date will remain in the low-dose aspirin group, and similarly for the non-aspirin group.

Outcomes

The primary outcomes of this study were the development of either CRC, GC, or EC. The follow-up period started from the date of first prescription of either low-dose aspirin or paracetamol (i.e. index date) and was censored at the incident diagnosis of any cancer, death, or end of study period (December 31, 2017). Patients diagnosed with CRC, GC, and EC were identified using International classification of diseases 9th revision (ICD-9) codes **(Supplementary Table 1)**. The secondary outcome was GIB that led to a hospital visit (diagnosis code for an in-patient, out-patient or accident and emergency room visit). The follow-up period started from the index date and was censored at diagnosis of the outcome, death or end of study period.

Study variables

Potential confounders included patient demographics (age, sex), comorbidities (diabetes mellitus, hyperlipidemia, hypertension, obesity, alcohol related disorders, congestive heart failure, arrhythmia and conduction disorders, arterial disease, valve disorders, cardiomyopathy, chronic kidney disease, hepatic failure, chronic obstructive pulmonary

disease [COPD], thyroid disorders, schizophrenia, depression, bipolar disorder, peptic ulcer, gastrointestinal reflux, irritable bowel syndrome, inflammatory bowel syndrome, and bleeds that led to hospitalization within one year prior to index date), and concomitant medication use one year prior to index date (nonsteroidal anti-inflammatory drugs [NSAIDs], antiplatelets, anticoagulants, oral hypoglycemic agents, insulin, diuretics, antihypertensive agents, anti-arrhythmic, calcium channel blockers, beta-blockers, angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor, peripheral vasodilators, lipid-lowering drugs, oral bisphosphonates, oral corticosteroids, proton pump inhibitors [PPI]/histamine-2 receptor blockers (H2-blockers), antidepressants, and antipsychotics).

Although evidence indicates a potential chemoprotective role of estrogens on the risk of certain cancers a prescription of estrogens (either as oral contraceptive or menopausal hormone) was not included as a study variable due to the small number of patients with an estrogen therapy (233 [0.47%] and 244 [0.49%] in low-dose aspirin and paracetamol users respectively).

Statistical analysis

Baseline characteristics of low-dose aspirin users and non-aspirin users were presented as frequencies (percentages) for categorical variables and as mean (±SD) for continuous variables. To reduce confounding arising from baseline differences between low-dose aspirin and non-aspirin users, propensity score (PS) matching was performed. Aforementioned confounders were included in estimating the PS value. Patients using low-dose aspirin and paracetamol were matched at a 1:1 ratio using a nearest neighbor algorithm with a caliper of 0.01. Standardized mean difference (SMD) <0.1 between treatment groups was considered acceptable/negligible.

The ratio of incidence per 1000-person years of CRC, GC, and EC among low-dose aspirin users and non-aspirin users was reported. The association of CRC, GC, and EC with the use of low-dose aspirin was estimated using competing risk Cox regression with death as the competing risk, and hazard ratio (HR) with 95% confidence interval (CI) was reported. The association of GIB with the use of low-dose aspirin was estimated using a Cox regression and HR with 95% CI was reported. The number needed to treat (NNT) and number needed to harm (NNH) was estimated using the equation; 1/absolute risk reduction and 1/absolute risk increase respectively.

Subgroup analysis was performed to investigate the risk of GI cancer and GIB in low-dose aspirin and non-aspirin users with different age groups (40-49 years old, 50-59 years old, 60-69 years old, 70-79 years old, and ≥80 years old). Since the use of gastroprotective agents (PPI/H2-blockers) could reduce the risk of GIB in patients on antithrombotic agents,[18] we assessed the association of GI cancer and GIB with the use of low-dose aspirin in patients on gastroprotective agents. As people with diabetes are at higher risk of developing cancer[19], we also evaluated the association of low-dose aspirin with GI cancer and GIB among this population. Lastly, the association between low-dose aspirin and GIB has been shown to be different depending on the location of the GIB. Therefore, we stratified the GIB outcome to upper GIB (UGIB) and lower GIB (LGIB).

Sensitivity analyses were conducted by excluding patients with cancer diagnosis during the first year of follow-up since the cancer could have developed before the start of follow-up. Patients with an ASCVD diagnosis during the first year of follow-up were removed to ensure all patients included have no pre-existing ASCVD. Non-aspirin users with a low-dose aspirin prescription during follow-up were censored at the first aspirin prescription. Lastly, the effectiveness of low-dose aspirin for GI cancer prevention was evaluated in patients taking

low-dose aspirin for secondary ASCVD prevention; patients taking low-dose aspirin for primary and secondary ASCVD were included.

R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. The analyses were conducted by JS and cross-checked independently by JZ for quality assurance.

Patient and public involvement

There was no patient and public involvement.

Results

Baseline characteristics

We identified 324 568 aspirin and 420 000 non-aspirin users between January 1, 2004 and December 31, 2008. Following exclusion criteria, 428 159 patients were eligible for the PS matching **(Figure 1).** A total of 99 358 individuals (49 679 low-dose aspirin users and 49 679 matched non-aspirin users) were successfully matched (**Supplementary Figure 1)**. After matching, all baseline characteristics had SMD < 0.1 and were well balanced. The mean (standard deviation [SD]) age for the cohort was 68.6 (12.6) years, and 48 022 (48.4%) were women **(Table 1).** The median (interquartile range [IQR]) follow-up for the cohort was 10.0 (6.4) years for the GI cancer outcome (9.8 [6.3] years low-dose aspirin users and 10.4 [6.3] years non-aspirin users), and 10.2 (5.9) years for the GIB outcome (9.9 [6.1] years low-dose aspirin users and 10.6 [5.7] years non-aspirin users)**.** The most common dose of aspirin was 80 mg daily (72.2%).

Risk of Gastrointestinal Cancer

In the propensity score-matched sample, 1954 of 99 358 participants developed CRC (876 low-dose aspirin users [1.7%] and 1078 non-aspirin users [2.2%]), 515 GC (222 [0.4%] and 293 [0.6%]), and 206 EC (96 [0.2%] and 110 [0.2%], respectively; **Table 2**). The results for the unmatched cohort are presented in **Supplementary Table 3**. The number of patients who died due to CRC, GC and EC were 247 (28.2%), 99 (44.6%) and 51 (53.1%) in low-dose aspirin users respectively, and 360 (33.4%), 151 (51.5%) and 55 (50.0%) in non-aspirin users respectively. NNT is 250 and 500 for CRC and GC respectively, and the NNH is 125 for GIB.

The results from the competing risk survival analysis showed that low-dose aspirin use was significantly associated with a lower risk of CRC and GC compared to non-aspirin users (CRC: HR, 0.83 [95% CI, 0.76-0.91]; GC: 0.77 [0.65-0.92]), but not with EC (HR, 0.88 [95% CI, 0.67-1.16]; **Table 2**). The association with lower risk was statistically significant for females (CRC: HR, 0.79 [95% CI, 0.68-0.90]; GC: 0.73 [0.54-0.98]) and males (CRC: HR, 0.86 [95% CI, 0.76-96]; GC: 0.79 [0.64-0.98]). The use of low-dose aspirin was significantly associated with a lower risk of CRC in patients aged between 70 to 79 years old (HR, 0.82 [95% CI, 0.71-0.94]) and among patients with diabetes (HR, 0.73 [95% CI, 0.57-0.94]), with a lower risk of GC among patients 80 years and older (HR, 0.60 [95% CI, 0.43-0.84]; **Table 2**).

There was no significant association between low-dose aspirin and esophageal cancer in any of the subgroup analysis (**Table 2**). The test for the interaction effect of low-dose aspirin and gastroprotective agents was not significant when assessing the association between low-dose aspirin and gastrointestinal cancer, with and without gastroprotective agents (*P* value for interaction, >0.5).

Risk of Gastrointestinal Bleeding

In the propensity score-matched sample, 10 629 of 99 358 participants had a GIB event (5498 low-dose aspirin users [11.1%] and 5131 non-aspirin users [10.3%]; **Table 3**). Among patients with a GIB diagnosis the number of patients who died due to a GIB was 88 (1.6%) in low-dose aspirin users and 83 (1.6%) in non-aspirin users. Compared to non-aspirin users, low-dose aspirin was significantly associated with an increased risk of GIB (HR, 1.15 [95% CI, 1.11-1.20]). The association with higher risk was statistically significant for females (HR, 1.16 [95% CI, 1.10-1.23]) and males (HR, 1.15 [95% CI, 1.09-1.21]), in addition to patients

aged 60 to 69 (HR, 1.13 [95% CI, 1.03-1.23]), 70 to 79 (HR, 1.44 [95% CI, 1.35-1.53]), and 80 years and older (HR, 1.18 [95% CI, 1.11-1.27].

Low-dose aspirin was not significantly associated with an increased risk of GIB in patients aged 40 to 49 (HR, 0.94 [95% CI, 0.77-1.15]) and 50 to 59 (HR, 1.05 [95% CI, 0.93-1.19]) as well as in patients with diabetes (HR, 1.07 [95% CI, 0.97-1.18]) and those taking gastroprotective agents (HR, 1.03 [95% CI, 0.96-1.10]; **Table 3**). The test for subgroup difference indicated significant difference between the association with and without gastroprotective agents (*P* value for interaction <0.001) (**Supplementary Table 4)**.

Low-dose aspirin was significantly associated with an increased risk of UGIB (HR, 1.14 [95% CI, 1.09-1.18]) and LGIB (HR, 1.31 [95% CI, 1.16-1.48]). The association with higher risk remained for LGIB among patients taking gastroprotective agents (HR, 1.70 [95% CI, 1.35-2.14]), however, low-dose aspirin was not associated with an increased risk of UGIB in those taking gastroprotective agents (HR, 0.98 [95% CI, 0.91-1.05]).

Sensitivity analysis

After removing patients with a cancer diagnosis during the first year of follow-up, the association remained similar for CRC (HR, 0.88 [95% CI, 0.80-0.96]), GC (HR, 0.76 [95% CI, 0.63-0.93]), and EC (HR, 1.13 [95% CI, 0.83-1.55]; **Figure 2).** The association with lower risk also remained after removing patients with a diagnosis of ASCVD during the first year of follow-up for CRC (HR, 0.90 [95% CI, 0.82-0.99]), GC (HR, 0.78 [95% CI, 0.66-0.94]), and EC (HR, 0.70 [95% CI, 0.53-0.94]). Lastly, the lower risk remained when censoring non-aspirin users at the first aspirin prescription during follow-up in CRC (HR, 0.88 [95% CI, 0.80-0.96]), and GC (HR, 0.80 [95% CI, 0.67-0.96]) but not EC (HR, 0.93 [95% CI, 0.71-1.23]). After combining all patients taking low-dose aspirin for either primary or secondary prevention of ASCVD, they had a lower risk of CRC (HR, 0.89 [95% CI, 0.83-

0.96]), GC (HR, 0.78 [95% CI, 0.69-0.89]), as well as EC (HR, 0.73 [95% CI, 0.60-0.90]) compared to non-aspirin users.

Discussion

In Chinese adults without pre-existing ASCVD, our results suggest that the use of low-dose aspirin was associated with a lower risk of CRC and GC, but not EC, as compared to non-aspirin users during a median follow-up of 10 years. However, low-dose aspirin was associated with an increased risk of GIB. Nevertheless, a subgroup analysis showed that the use of low-dose aspirin was not associated with an increased risk of GIB among patients younger than 60 years old and those taking PPIs or H2-blockers.

Our findings are consistent with a meta-analysis of patient follow-up (maximum duration 20 years) from five RCTs which showed that aspirin was associated with a reduced risk of colorectal cancer (HR 0.76; 95% CI = 0.60-0.96).[8] In addition to RCTs, observational studies have also examined the association of low-dose aspirin with GI cancer.[20-27] Although studies have consistently shown a beneficial effect of using low-dose aspirin, findings from both RCTs and observational studies have largely been limited to Caucasians.[20 22-24 27] An earlier study in Hong Kong evaluated the risk of GIB and benefit of CRC reduction from the use of low-dose aspirin and found that low-dose aspirin lowered the risk of CRC but at the cost of a higher risk of GIB. The authors acknowledged that the results could be inaccurate due to confounding by indication since no comorbidities were used to adjust for baseline differences between aspirin and non-aspirin users.[28] Our present study adjusted for observed baseline differences between aspirin and non-aspirin users by using PS matching. Moreover, most studies include patients taking low-dose aspirin for both primary and secondary prevention of ASCVD. However, the clinical implications for the primary prevention cohort is greater as initiating low-dose aspirin is no longer standard practice for this population.

A study in the United Kingdom has evaluated the protective effect of low-dose aspirin on CRC in a cohort with no pre-existing CVD.[4] However, the risk of GIB was not investigated.

Nevertheless, the association of low-dose aspirin with a reduced risk of GI cancer was consistent with our findings. Furthermore, our findings are also consistent with our recent 13-year cohort study conducted in Hong Kong (N=74 161) which found that regular aspirin use was associated with a decrease in gastric cancer risk following *Helicobacter pylori* eradication.[16] Daily use, prolonged use, and use of higher doses of aspirin after *Helicobacter pylori* eradication was associated with significant reduction in the risk of gastric cancer.[16]

The role of low-dose aspirin for the prevention of GI cancer is equivocal and questions remain, particularly for patients without a history of ASCVD. Some RCTs have reported no reductions in GI cancer incidence and mortality with the use of low-dose aspirin. [5 7] The Aspirin in Reducing Events in the Elderly (ASPREE) trial reported a higher mortality rate in patients taking low-dose aspirin compared to placebo. A secondary analysis showed cancer as the major contributor to the higher mortality rate (HR: 1.13; 1.10-1.56), with a subgroup analysis for GI cancer which detected no differences between groups (CRC: RR, 0.97 [0.77-1.24]).[6] Patients in the ASPREE trial were ≥70 years old, hence the benefits of low-dose aspirin for GI cancer prevention may be limited since most of the benefits of low-dose aspirin are apparent in studies of younger adults with longer duration of use.[29] Notably, Asians comprised only 1% of the trial population in ASPREE. Therefore, findings from ASPREE may be more applicable to healthy Caucasian adults.

Potential clinical implications

The finding that low-dose aspirin use was associated with a lower risk of CRC and GC is of particular clinical importance, especially among patients with no pre-existing ASCVD, since the decision to initiate low-dose aspirin is less well defined. GI cancers are major contributors to mortality worldwide with no proven preventative treatment. Aspirin is affordable, easily accessible and has a recognized pharmacological profile which could be a means to

improving the burden of disease. Additionally, the risk of GIB associated with low-dose aspirin is of particular interest in the Chinese population, which has a different bleeding profile compared to Caucasians.[14] Lastly, our study showed that for every 1000 patients taking low-dose aspirin, 6 GI cancer cases could be prevented, although it could cause 8 GIBs. However, the percentage of patients with GI cancer outcome who died was 30% to 50% compared to 1.6% for GIB. In addition, the percentage of fatal GIB (1.6%) is similar in both the low-dose aspirin and non-aspirin group. This indicates that the use of low-dose aspirin does not contribute to an increase in the risk of fatal GIB. Further, this is consistent with a meta-analysis published in 2016 which evaluated fatal GIB attributable to low-dose aspirin.[30] This information along with the knowledge that patients under 60 years or those taking gastroprotective agents are not at higher risk of GIB could inform clinical decisions to initiate low-dose aspirin in Chinese adults without ASCVD who highly value preventing CRC and GC.

Strengths and limitations

To our knowledge, this is the first study to evaluate the association of low-dose aspirin with GI cancer and GIB among patients without ASCVD. The findings are likely generalizable to other urban Chinese populations with similar risks of GI cancer as the population of Hong Kong. We used PS matched cohort study to emulate a target randomized trial since the feasibility of an RCT is low due to the large sample size and long follow-up that is required to evaluate cancer outcomes. Furthermore, while low-dose aspirin is a non-prescription medication in Hong Kong, its cost is heavily subsidized ($15 HKD ~ $2 USD for 4-month supply) through the public healthcare system. Thus, misclassification of exposure to low-dose aspirin is likely minimal.[14]

This study has several limitations. Similar to some electronic health record databases, information such as body mass index, smoking status, and alcohol consumption are not routinely recorded in CDARS. However, other confounders were used as proxy to account for these risk factors (COPD and alcohol related disorders). A general limitation of cohort studies is the residual and the unmeasured confounding bias which cannot be excluded. Finally, subgroup analyses by age, diabetes mellitus, and use of gastroprotective agents should be interpreted as hypothesis generating results since the low number of events upon stratification resulted in limited statistical power.

Our findings support a potential role for low-dose aspirin therapy for the prevention of colorectal and gastric cancer, but not esophageal cancer, in Chinese adults ≥40 years. Further research, such as a pragmatic RCT, is needed to confirm the observed association in a patient population that would be expected to derive the most benefit, and least harm, from taking low-dose aspirin.

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Data sharing

No additional data are available.

Author contributions

Dr. Chan and Ms. Shami had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Shami, Zhao, Chan, Wong.

Acquisition, analysis, or interpretation of data: Shami, Zhao, Pathadka, Wan, Chan, Wong.

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Critical revision of the manuscript for important intellectual content: Shami, Zhao, Pathadka, Wan, Blais, Cheung, Leung, Wong, Chan..

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Supervision: Chan, Wong.

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Conflict of interest

Dr Chan has received honorarium from the Hospital Authority and research funding from The Hong Kong Research Grants Council, The Research Fund Secretariat of the Food and Health Bureau, Narcotics Division of the Security Bureau of HKSAR, Hong Kong; National Natural Science Fund of China, China; Wellcome Trust, United Kingdom; Bristol-Myers Squibb, Pfizer, and Takeda, for work unrelated to this study. Professor Wong has received research funding outside the submitted work from the Hong Kong Research Grants Council and the Hong Kong Health and Medical Research Fund, National Institute for Health Research in the UK, European Commission, Amgen, Bayer, Bristol-Myers Squibb, GSK, and Janssen. Mr. Vora and Ms. Soriano-Gabarro are employees of Bayer AG. The remaining authors have no conflict of interest to declare.

Transparency declaration

Ms. Jessica Shami affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Jessica Shami

Dissemination declaration

Dissemination to study participants and or patient organizations is not possible.

License statement

relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Ethics statement

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number: UW 18-033). Informed patient consent was not required as the data used in this study were anonymized.

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Tables

Table 1. Baseline Characteristics of Low-Dose Aspirin and Paracetamol Users[a]

Characteristics	Before Propensity Score Matching			After Propensity Score Matching		
	Low-dose Aspirin (n=60 869)	Paracetamol (n=367 290)	Standardized Difference [b]	Low-dose Aspirin (n=49 679)	Paracetamol (n=49 679)	Standardized Difference [b]
Age, mean (SD), y	69.1 (12.5)	57.6 (12.8)	0.912	68.0 (12.5)	69.1 (12.7)	0.09
Female	29 010 (47.7)	211 841 (57.7)	0.202	24 031 (48.4)	23 991 (48.3)	0.002
Aspirin dose						
≤100 mg	52 125 (85.6)	-	-	42 756 (86.1)	-	-
101 mg – 200 mg	7396 (12.2)	-	-	5909 (11.9)	-	-
200 mg – 300 mg	1348 (2.2)	-	-	1014 (2.0)	-	-
Medical conditions						
Hypertension	12 679 (20.8)	18 469 (5.0)	0.485	8651 (17.4)	8626 (17.4)	0.001
Congestive heart failure	3676 (6.0)	1568 (0.4)	0.321	1734 (3.5)	1289 (2.6)	0.05
Arrhythmia and conduction disorders	8397 (13.8)	3563 (1.0)	0.506	3915 (7.9)	2900 (5.8)	0.08
Arterial disease	601 (1.0)	578 (0.2)	0.110	378 (0.8)	321 (0.6)	0.01
Valve disorders	436 (0.7)	579 (0.2)	0.085	266 (0.5)	254 (0.5)	0.003
Cardiomyopathy	329 (0.5)	149 (0.0)	0.093	165 (0.3)	114 (0.2)	0.02
Diabetes mellitus	9079 (14.9)	12 148 (3.3)	0.412	6079 (12.2)	5975 (12.0)	0.006
Hyperlipidemia	2130 (3.5)	2662 (0.7)	0.194	1400 (2.8)	1325 (2.7)	0.009
Thyroid disorders	1189 (2.0)	4644 (1.3)	0.055	851 (1.7)	837 (1.7)	0.002
Major bleeding	408 (0.7)	1269 (0.3)	0.046	316 (0.6)	343 (0.7)	0.007
COPD	2868 (4.7)	6214 (1.7)	0.172	2062 (4.2)	2109 (4.2)	0.005
Obesity	214 (0.4)	358 (0.1)	0.054	139 (0.3)	144 (0.3)	0.002
CKD	1359 (2.2)	1343 (0.4)	0.165	801 (1.6)	737 (1.5)	0.01
Chronic liver disease	544 (0.9)	1953 (0.5)	0.043	437 (0.9)	462 (0.9)	0.005
GERD	150 (0.2)	410 (0.1)	0.032	105 (0.2)	115 (0.2)	0.004

Irritable bowel syndrome	45 (0.1)	293 (0.1)	0.002	37 (0.1)	41 (0.1)	0.003
Peptic ulcer	244 (0.4)	952 (0.3)	0.025	193 (0.4)	186 (0.4)	0.002
Inflammatory bowel disease	11 (0.0)	106 (0.0)	0.007	10 (0.0)	8 (0.0)	0.003
Alcoholism	1166 (1.9)	3005 (0.8)	0.095	826 (1.7)	836 (1.7)	0.002
Schizophrenia	1125 (1.8)	5699 (1.6)	0.023	900 (1.8)	916 (1.8)	0.002
Bipolar disorder	95 (0.2)	706 (0.2)	0.009	87 (0.2)	98 (0.2)	0.005
Depression	1158 (1.9)	6291 (1.7)	0.014	943 (1.9)	942 (1.9)	<0.001
Medications						
Diuretics	14 350 (23.6)	28 961 (7.9)	0.441	10 042 (20.2)	10 136 (20.4)	0.005
ACE inhibitor or ARB	16 819 (27.6)	20 267 (5.5)	0.623	11 195 (22.5)	11 003 (22.1)	0.009
Other antihypertensives	8785 (14.4)	18 471 (5.0)	0.321	6384 (12.9)	6676 (13.4)	0.02
CCB	22 514 (37.0)	45 062 (12.3)	0.599	16 622 (33.5)	17 637 (35.5)	0.04
Anti-arrhythmic	1562 (2.6)	1335 (0.4)	0.184	760 (1.5)	537 (1.1)	0.04
Beta-blockers	21 756 (35.7)	42 667 (11.6)	0.592	15 777 (31.8)	16 466 (33.1)	0.03
Peripheral vasodilators	741 (1.2)	598 (0.2)	0.128	435 (0.9)	373 (0.8)	0.01
Oral hypoglycemic	14 789 (24.3)	25 443 (6.9)	0.493	10 799 (21.7)	11 260 (22.7)	0.02
Insulin	3321 (5.5)	2686 (0.7)	0.275	1972 (4.0)	1790 (3.6)	0.02
Lipid lowering drugs	10 680 (17.5)	10 362 (2.8)	0.502	7019 (14.1)	6835 (13.8)	0.01
PPI or H2-blockers	21 143 (34.7)	39 028 (10.6)	0.601	14 323 (28.8)	13 898 (28.0)	0.02
NSAID	8324 (13.7)	62 026 (16.9)	0.089	7137 (14.4)	7503 (15.1)	0.02
Oral bisphosphonates	245 (0.4)	455 (0.1)	0.054	182 (0.4)	186 (0.4)	0.001
Oral corticosteroids	7561 (12.4)	30 915 (8.4)	0.131	5913 (11.9)	6136 (12.4)	0.01
Anticoagulants	2537 (4.2)	1359 (0.4)	0.257	1278 (2.6)	962 (1.9)	0.04
Antiplatelet	1408 (2.3)	328 (0.1)	0.205	532 (1.1)	316 (0.6)	0.05
Antipsychotics	2172 (3.6)	7718 (2.1)	0.088	1664 (3.3)	1708 (3.4)	0.005
Antidepressants	2583 (4.2)	10 947 (3.0)	0.068	2063 (4.2)	2110 (4.2)	0.005

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitors.

[a] Values are expressed as frequency (%) unless otherwise specified. [b] Standardized difference indicates difference in mean or proportion of covariates in the low-dose aspirin group vs the paracetamol group divided by the pooled standard deviation.

Table 2. Risk of Gastrointestinal Cancers with Low-Dose Aspirin and Paracetamol After Propensity Score Matching

	Low-dose Aspirin			Paracetamol				
	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	HR (95% CI)	*P* Value
Colorectal cancer	49 679	876/428 554	2.04	49 679	1078/457 195	2.36	0.83 (0.76-0.91)	<.001
Female	24 031	356/211 588	1.68	23 991	463/226 257	2.05	0.79 (0.68-0.90)	<.001
Male	25 648	520/216 966	2.40	25 688	615/230 938	2.66	0.86 (0.76-0.96)	.01
40-49 years old	4344	15/45 459	0.33	4002	26/44 565	0.58	0.57 (0.30-1.06)	.08
50-59 years old	9350	90/95 162	0.95	8416	105/91 025	1.15	0.84 (0.63-1.11)	.20
60-69 years old	11 489	224/110 070	2.04	11 050	250/112 834	2.22	0.89 (0.74-1.07)	.19
70-79 years old	14 976	352/123 565	2.85	15 326	446/139 167	3.20	0.82 (0.71-0.94)	.004
≥80 years old	9520	195/54 298	3.59	10 885	251/69 604	3.61	0.89 (0.74-1.07)	.23
Diabetes Mellitus	6079	108/46 923	2.30	5975	147/49 238	2.99	0.73 (0.57-0.94)	.01
PPI/H2 blocker use	14 323	224/112 848	1.98	13 898	262/120 357	2.18	0.85 (0.71-1.02)	.07
Gastric cancer	49 679	222/428 554	0.52	49 679	293/457 195	0.64	0.77 (0.65-0.92)	.003
Female	24 031	73/211 591	0.35	23 991	103/226 259	0.46	0.73 (0.54-0.98)	.04
Male	25 648	149/216 969	0.69	25 688	190/230 940	0.82	0.79 (0.64-0.98)	.03
40-49 years old	4344	5/45 459	0.11	4002	8/44 565	0.18	0.58 (0.19-1.77)	.34
50-59 years old	9350	31/95 162	0.33	8416	21/91 025	0.23	1.40 (0.80-2.45)	.24
60-69 years old	11 489	41/110 070	0.37	11 050	52/112 834	0.46	0.78 (0.51-1.17)	.22
70-79 years old	14 976	93/123 565	0.75	15 326	113/139 167	0.81	0.85 (0.65-1.12)	.26
≥80 years old	9520	52/54 298	0.96	10 885	99/69 604	1.42	0.60 (0.43-0.84)	.003
Diabetes Mellitus	6079	28/46 923	0.60	5975	40/49 238	0.81	0.69 (0.43-1.13)	.14
PPI/H2 blocker use	14 323	65/112 848	0.58	13 898	82/120 357	0.68	0.77 (0.56-1.07)	.12
Esophageal cancer	49 679	96/428 554	0.22	49 679	110/457 195	0.24	0.88 (0.67-1.16)	.37
Female	24 031	23/211 591	0.11	23 991	29/226 259	0.13	0.80 (0.46-1.39)	.43

Male	25 648	73/216 969	0.34	25 688	81/230 940	0.35	0.91 (0.66-1.25)	.55
40-49 years old	4344	2/45 459	0.04	4002	1/44 565	0.02	2.05 (0.22-19.5)	.53
50-59 years old	9350	11/95 162	0.12	8416	11/91 025	0.12	0.95 (0.41-2.19)	.90
60-69 years old	11 489	30/110 070	0.27	11 050	25/112 834	0.22	1.19 (0.70-2.02)	.53
70-79 years old	14 976	35/123 565	0.28	15 326	39/139 167	0.28	0.92 (0.58-1.45)	.72
≥80 years old	9520	18/54 298	0.33	10 885	34/69 604	0.49	0.61 (0.34-1.07)	.08
Diabetes Mellitus	6079	13/46 923	0.28	5975	19/49 238	0.39	0.67 (0.33-1.36)	.27
PPI/H2 blocker use	14 323	28/112 848	0.25	13 898	29/120 357	0.24	0.94 (0.56-1.58)	.82

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitors.

Table 3. Risk of Gastrointestinal Bleeding with Low-Dose Aspirin and Paracetamol After Propensity Score Matching

	Low-dose Aspirin			Paracetamol				
	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	HR (95% CI)	*P* Value
Overall	49 679	5498/431 246	12.27	49 679	5131/465 091	11.03	1.15 (1.11-1.20)	<.001
Female	24 031	2698/212 596	12.69	23 991	2510/229 792	10.92	1.16 (1.10-1.23)	<.001
Male	25 648	2800/218 650	12.81	25 688	2621/235 300	11.14	1.15 (1.09-1.21)	<.001
40-49 years old	4344	184/46 633	3.95	4002	190/45 506	4.18	0.94 (0.77-1.15)	.56
50-59 years old	9350	526/97 488	5.40	8416	476/93 363	5.10	1.05 (0.93-1.19)	.41
60-69 years old	11 489	1007/112 395	8.96	11 050	935/116 577	8.02	1.13 (1.03-1.23)	.008
70-79 years old	14 976	2153/122 814	17.53	15 326	1742/141 851	12.28	1.44 (1.35-1.53)	<.001
≥80 years old	9520	1628/51 916	31.36	10 885	1788/67 795	26.37	1.18 (1.11-1.27)	<.001
Diabetes Mellitus	6079	756/46 398	16.29	5975	752/49 701	15.13	1.07 (0.97-1.18)	.20
PPI/H2 blocker use	14 323	1682/113 597	14.81	13 898	1738/122 015	14.24	1.03 (0.96-1.10)	.46
Upper GIB	49 679	4964/431 246	11.51	49 679	4649/465 091	10.00	1.14 (1.09-1.18)	<.001
PPI/H2 blocker use	14 323	1513/113 597	13.32	13 898	1612/122 015	13.21	0.98 (0.91-1.05)	.54
Lower GIB	49 679	549/431 246	1.27	49 679	501/465 091	1.08	1.31 (1.16-1.48)	<.001
PPI/H2 blocker use	14 323	176/113 597	1.55	13 898	131/122 015	1.07	1.70 (1.35-2.14)	<.001

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitors.

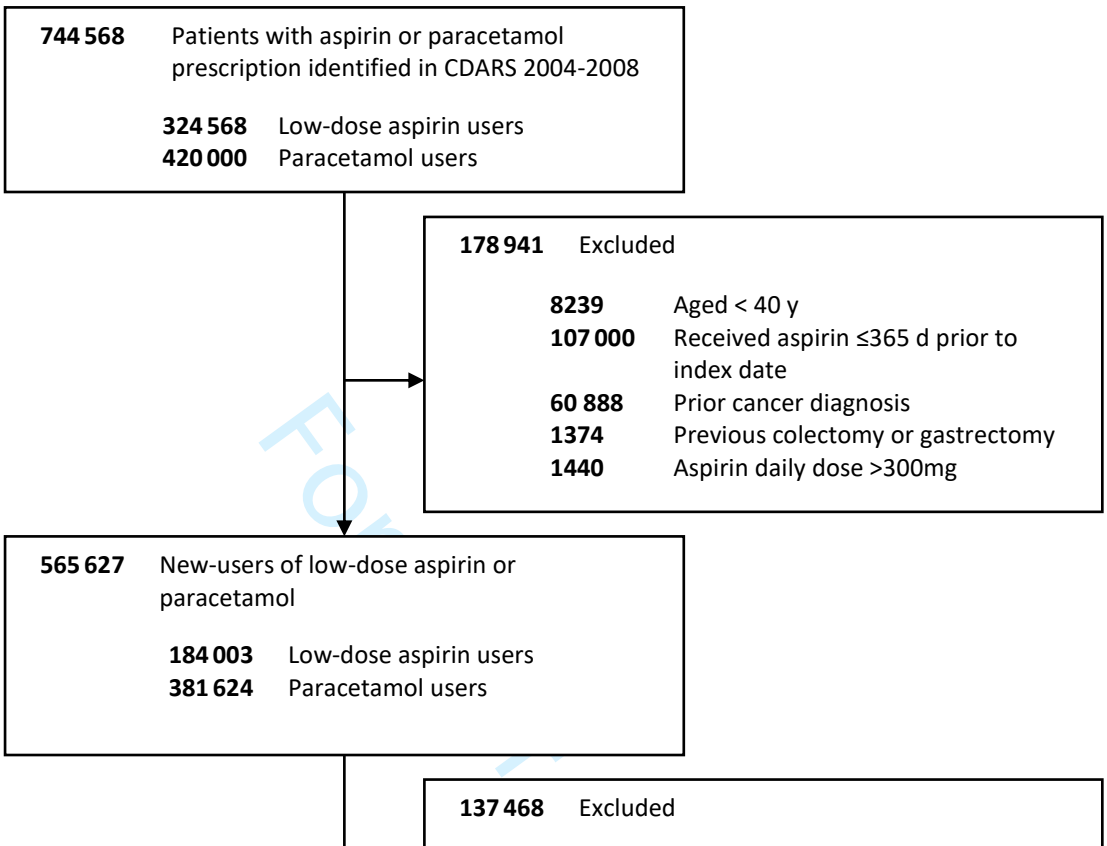
Figure legends

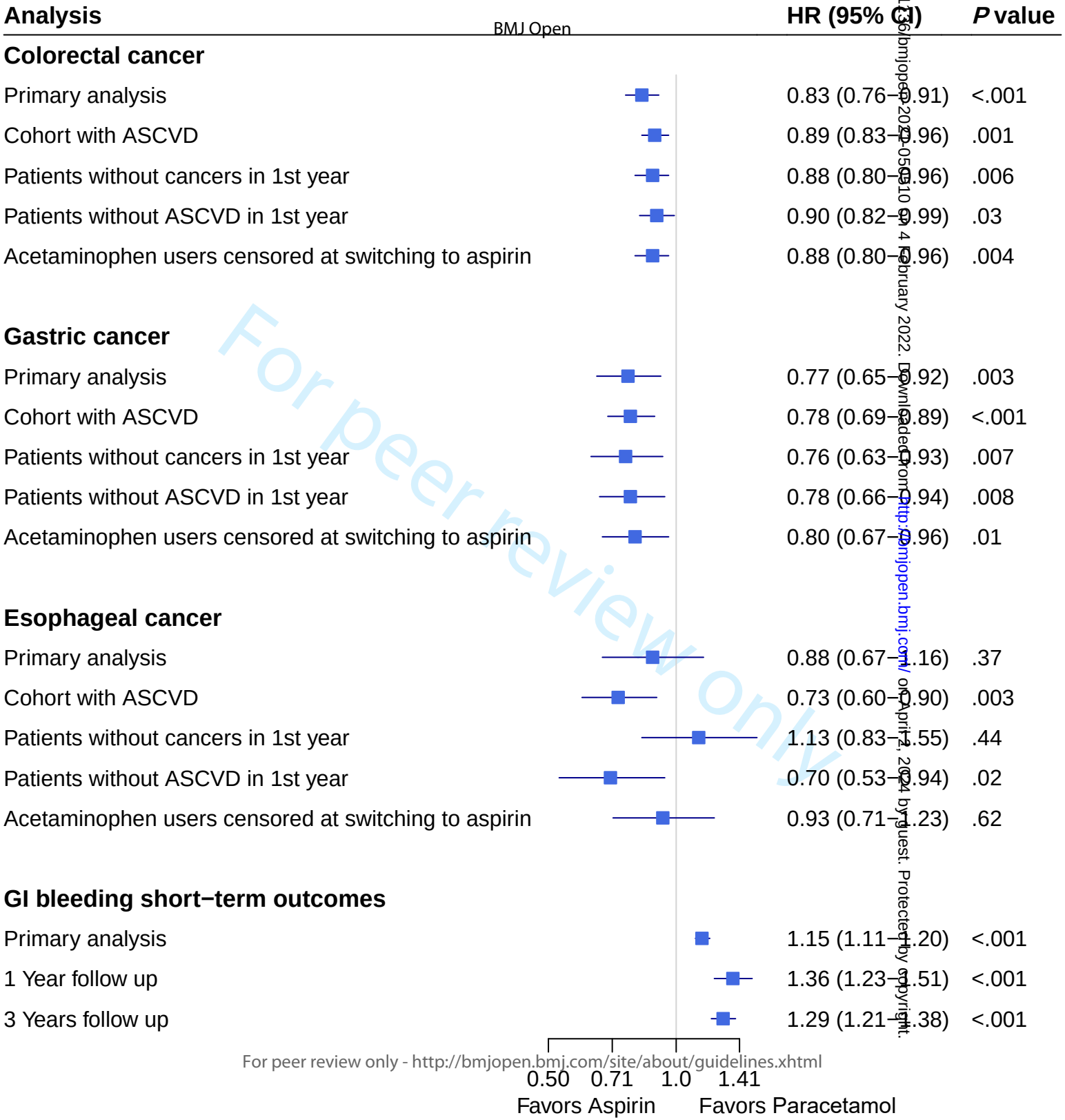
Figure 1. Flow chart of users in the cohort study assessing the risk of gastrointestinal cancer and gastrointestinal bleeding

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CDARS, Clinical Data Analysis and Reporting System (of the Hong Kong Hospital Authority); PS, propensity score.

Figure 2. Forest plot of the results of the primary and sensitivity analyses

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; GI, gastrointestinal bleeding; HR, hazard ratio.





Supplementary Material

Supplementary Table 1. List of diagnosis and procedure codes used in the study

Supplementary Table 2. List of drug names and codes used in the study

Supplementary Table 3. Risk of gastrointestinal cancers and gastrointestinal bleeding with low-dose aspirin and paracetamol before propensity score matching

Supplementary Table 4. Number of patients with a prescription of proton pump inhibitors and H2 receptor antagonists during baseline

Supplementary Figure 1. Propensity score plot before and after matching

Supplementary Table 1. List of diagnosis and procedure codes used in the study

Baseline characteristics	**ICD-9 codes**
Hypertension	401 – 405
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428
Arrhythmia and conduction disorders	426-427
Arterial disease	433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 440-445, 447, 557
Valve disorders	424
Cardiomyopathy	425
Diabetes mellitus	250
Hyperlipidemia	272.0-272.2, 272.4
Thyroid disorders	242-244
Major bleeding^	531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 578.0, 578.1, 578.9, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 569.86, 430, 431, 432.
COPD	490-492, 494, 496
Obesity	278
CKD	585
Chronic liver disease	570, 571
GERD	530.81
Irritable bowel syndrome	564.1
Peptic ulcer	533
Inflammatory bowel disease	556
Alcohol related disorders	265.2, 291.1, 291.2, 291.3, 291.5, 291.6, 291.7, 291.8, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.1, 571.2, 571.3, 980, V11.3
Schizophrenia and psychosis	295, 297, 298.3, 298.4, 298.8, 298.9
Bipolar disorder	296.0, 296.1, 296.4-296.7, 296.80, 296.81 296.89
Depression	296.2, 296.3, 296.82, 298.0, 300.4, 311
Outcomes	**ICD-9 codes**
Colorectal cancer	153, 154
Gastric cancer	151
Esophageal cancer	150
Gastrointestinal bleeding	531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 578.0, 578.1, 578.9, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 569.86

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease.

^ Major bleeding; bleeding that led to hospitalization in the last 365 days

Supplementary Table 2. List of drug names and codes used in the study

Baseline characteristics	Drug item code	Drug name
NSAIDs	CELE, DICL, SULI, PIRO, IBUP, NAPR, INDO02-03, ETOR, MELO	Celecoxib, Diclofenac, Sulindac, Piroxicam, Ibuprofen, Naproxen, Indomethacin, Etoricoxib, Meloxicam
Antiplatelet	ABCI, CLOP, DIPY, EPTI, TICA, PRAS	Dipyridamole, Clopidogrel, Prasugrel, Ticagrelor, Abciximab, Eptifibatide
Anticoagulants	APIX, DABI, EDOX, ARGA, WARF, HEPA03-04-05-11, TINZ, NADR, ENOX, EPOP	Apixaban, Dabigatran, Rivaroxaban, Edoxaban, Argatroban, Warfarin, Heparin, Tinzaparin, Nadroparin, Enoxaparin, Epoprostenol
Insulin	INSU	Biphasic Insulin Aspart, Biphasic Insulin Lispro, Insulin Human, Insulin Isophane Human, Insulin Neutral Human, Insulin Aspart Human, Insulin Degludec, Insulin Detemir, Insulin Glargine, Insulin Glulisine, Insulin Lispro Human
Oral hypoglycemic drugs	ACAR, ALOG, DAPA, DEXT01,18,22,28, 43,35,36, 70,71,72,75,76,78, 82,84,90,99, DIAZ07, DULA, EMPA, EXEN, GLIC, GLIP, GLIM, GLUC01,37, LINA, LIRA, LIXI, METF01,02, PIOG, SAXA, SITA, VILD	Acarbose, Alogliptin, Dapagliflozin, Dextrose, Diazoxide, Dulaglutide, Empagliflozin, Exenatide, Gliclazide, Glipizide, Glimepiride, Glucagon, Linagliptin, Liraglutide, Lixisenatide, Metformin, Pioglitazone, Saxagliptin, Sitagliptin, Vildagliptin
Lipid lowering drugs	ATOR01-02-03-04, FLUV-02-03-05, LOVA, PRAV-01-02, ROSU01-02, SIMV-01-02-04-05, ALIR, CHOL, EVOL, EZET, FENO, GEMF	Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin, Alirocumab, Cholestyramine, Evolocumab, Ezetimibe, Fenofibrate, Gemfibrozil
PPI or H2-blockers	ARIP01-02, ESOM01-02-03, LANS01-02-03-04, OMEP01-02-05-06-07, PANT-01-02-03, RABE-01-02, FAMO, RANI01,03,05,07	Aripiprazole, Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole, Famotidine, Ranitidine
Oral bisphosphonates	ALEN, CLOD, IBAN, PAMI, RISE, ZOLE	Alendronate, Clodronate, Ibandronic acid, Pamidronate, Risedronate, Zoledronic acid
Antipsychotics	AMIS, ARIP, CHLOR, CLOZ, FLUP, RISP, HALO03, HALO05, HALO06, HALO07, HALO08, HALO09, HALO11, HALO13, HALO14, LITH, LURA, OLAN, PALI, PERI01, PERI02, PIMO, QUET, SULP19, SULP20, TRIF, ZIPR, ZUCL	Amisulpride, Aripiprazole, Chlorpromazine, Clozapine, Flupenthixol, Risperidone, Fluphenazine, Haloperidol, Lithium, Lurasidone, Olanzapine, Paliperidone, Pericyazine, Pimozide, Quetiapine, Sulpiride, Trifluoperazine, Ziprasidone, Zuclopenthixol
Antidepressants	AMIT, AGOM, BUPR06, CLOM01, CLOM02, DEAN, DOTH, DOXE, FLUP01, FLUP02, FLUP03, FLUP04, FLUP11, PARO, IMIP, MIAN, VORT, MIRT, MOCL, NORT, TRAZ, TRIM05, TRIM06, TRIM13	Amitriptyline, Agomelatine, Bupropion, Clomipramine, Deanxit, Dothiepin, Doxepin, Flupenthixol, Paroxetine, Imipramine, Mianserin, Vortioxetine, Mirtazapine,

		Moclobemide, Nortriptyline, Trazodone, Trimipramine
Oral corticosteroids	BETA04, BETA06, BETA07, BETA08, BETA09, BETA13, BETA16, DEXA, FLUD, HYDR06, HYDR07, HYDR08, HYDR11, HYDR13, HYDR28, HYDR40, HYDR41, HYDR54, HYDR56, HYDR59, HYDR60, HYDR61, PRED01, PRED02, PRED06, PRED08, PRED09, PRED14, PRED15, PRED16, PRED17, PRED19, PRED21, PRED22, PRED23, PRED26, PRED27, METH29, METH30, METH36, METH37, METH66, METH67, METH71, TRIA02, TRIA03, TRIA04, TRIA09, TRIA13	Betamethasone, Dexamethasone, Fludrocortisone, Hydrocortisone, Prednisolone, Triamcinolone
Diuretics	AMIL, BUME, DYAZ, EPLE, FRUS, HYDR05, HYDR30, HYDR38, INDA, MANN, METO05, MODU, SPIR	Amiloride, Bumetanide, Dyazide, Eplerenone, Frusemide, Hydrochlorothiazide, Indapamide, Mannitol, Metolazone, Moduretic, Spironolactone
Anti-arrhythmic	AMIO, ATRO, DISO02, DISO03, DRON, FLEC, MEXI, PROC03, PROP01, QUIN02	Miodarone, Atropine, Disopyramide, Dronedarone, Flecainide, Mexiletine, Procainamide, Propafenone, Quinidine
Beta-blockers	ATEN, BISO, CARV, ESMO, LABE, METO06, METO07, METO08, METO09, METO10, METO11, METO13, METO15, METO16, NADO, PIND, PROP04, PROP05, PROP07, PROP08, PROP13, SOTA	Atenolol, Bisoprolol, Carvedilol, Esmolol, Labetalol, Metoprolol, Nadolol, Pindolol, Propranolol, Sotalol
ACE inhibitor or ARB	CAND, CAPT, ENAL, IRBE, LISI, LOSA, PERI17, PERI18, RAMI, TELM, VALS	Candesartan, Captopril, Enalapril, Irbesartan, Lisinopril, Losartan, Perindopril, Ramipril, Telmisartan, Valsartan
Other antihypertensive	CLON05, DOXA, HYDR01, HYDR02, HYDR03, ILOP, METH22, METH23, METH78, NITR06, PHEN16, PRAZ03, PRAZ04, PRAZ05, TERA	Lonidine, Doxazosin, Hydralazine, Iloprost, Methyldopa, Nitroprusside, Phenoxybenzamine, Phentolamine, Prazosin, Terazosin
CCB	AMLO, DILT, FELO, LERC, NIFE, NIMO, VERA	Amlodipine, Diltiazem, Felodipine, Lercanidipine, Nifedipine, Nimodipine, Verapamil
Peripheral vasodilators	CILO, IVAB, NAFT02, NAFT03, NICE, OXPE	Cilostazol, Ivabradine, Naftidrofuryl, Nicergoline, Oxpentifylline

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitors.

Supplementary Table 3. Risk of gastrointestinal cancers and gastrointestinal bleeding with low-dose aspirin and paracetamol before propensity score matching

	Low-dose Aspirin			Paracetamol			Low-dose Aspirin vs Paracetamol	
	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	No.	No. of Cases/ Person-Years	Incidence per 1000 Person-Years	HR (95% CI)	*P* Value
Colorectal cancer	60 869	1085/498 618	2.18	367 290	4978/3 872 782	1.28	1.71 (1.60-1.83)	<.001
Gastric cancer	60 869	276/498 618	0.55	367 290	1223/3 872 782	0.32	1.74 (1.53-1.99)	<.001
Esophageal cancer	60 869	112/498 618	0.22	367 290	550/3 872 782	0.14	1.53 (1.25-1.88)	<.001
Gastrointestinal bleeding	60 869	7053/545 721	12.92	367 290	21 037/ 4 014 350	5.24	2.47 (2.40-2.54)	<.001

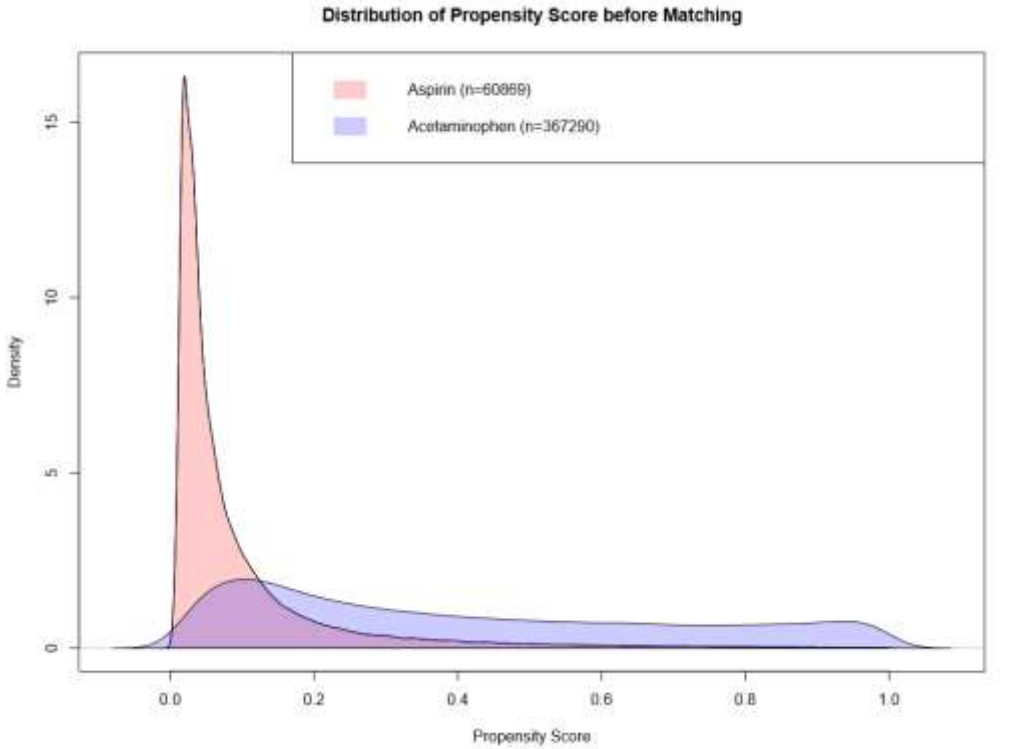
Abbreviations: CI, confidence interval; HR, hazard ratio.

Supplementary Table 4. Number of patients with a prescription of proton pump inhibitors and H2 receptor antagonists during baseline

	Low-dose aspirin users	***Paracetamol users***
Prescribed PPI or H2 blockers (%)	*14323 (28.8)*	*13,898 (28.0)*
PPI	3945 (27.5)	4317 (31.1)
Esomeprazole	1125 (28.5)	1342 (31.1)
20mg	774 (68.8)	667 (49.7)
40mg	351 (31.2)	675 (50.3)
Lansoprazole	409 (10.4)	502 (11.6)
15mg	21 (5.1)	38 (7.6)
30mg	388 (94.4)	464 (92.4)
Omeprazole	65 (1.6)	333 (7.7)
20mg	4 (5.7)	145 (43.5)
40mg	61 (94.3)	188 (56.5)
Pantoprazole	1081 (27.4)	1295 (30.0)
20mg	288 (26.6)	190 (14.7)
40mg	793 (73.4)	1105 (85.3)
Rabeprazole	1265 (32.1)	845 (19.6)
10mg	161 (12.7)	125 (14.8)
20mg	1104 (87.3)	720 (85.2)
H2 blockers	13230 (92.4)	13552 (97.5)
Famotidine	13118 (99.2)	12886 (95.1)
20mg	11491 (87.6)	11804 (91.6)
40mg	1627 (12.4)	1082 (8.4)
Ranitidine	112 (0.8)	666 (4.9)
150mg	110 (98.3)	661 (99.2)
400mg	2 (1.7)	5 (0.8)

Abbreviations: PPI, proton pump inhibitors; H2 blockers, Histamine-2 receptor antagonists.

Supplementary Figure 1. Propensity score plot before and after matching



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.