BMJ Open

Use of non-steroidal anti-inflammatory drugs and risk of gastrointestinal cancer

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-021869
Article Type:	Research
Date Submitted by the Author:	23-Jan-2018
Complete List of Authors:	Brusselaers, Nele; Karolinska Institutet, Molecular medicine and Surgery Lagergren, Jesper; Karolinska Institutet, Department of Molecular medicine and Surgery; King's College London, Division of Cancer Studies
Keywords:	Gastrointestinal tumours < GASTROENTEROLOGY, chemoprevention, non-steroidal antiinflammatory drugs, aspirin, coxibs, cancer

Use of non-steroidal anti-inflammatory drugs and risk of gastrointestinal cancer

Running title: NSAIDs and gastrointestinal cancer prevention

Authors: Nele BRUSSELAERS[1,2], MD MSc PhD, Jesper LAGERGREN[3,4], MD PhD.

Affiliations:

[1] Centre for Translational Microbiome Research, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Karolinska Hospital, Stockholm, Sweden

[2] Science for Life Laboratory (SciLifeLab), Stockholm, Sweden

[3] Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

[4] Division of Cancer Studies, King's College London, United Kingdom.

Correspondence and requests for reprints: Dr. Nele Brusselaers, Centre for Translational Microbiome Research, Department of Microbiology, Tumor and Cell biology, Karolinska Institutet, Nobelsvag16, 171 77 Stockholm, Sweden.
E-mail: Nele.Brusselaers@ki.se, Tel: +46 8 524 853 08
***Email addresses authors*:** nele.brusselaers@ki.se; jesper.lagergren@ki.se

Word count*:* 3,649 words; Tables: 5, Figures: 0; supplement: 3

Structured summary (228 words)

Objectives: Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are potential candidates for chemoprevention of gastrointestinal cancer. We aimed to assess the association between contemporary NSAID use (≥180 days) and gastrointestinal cancer.

Design: Nationwide Swedish population-based cohort study (2005-2012,

Setting: Sweden

Participants: All adults exposed to maintenance NSAIDs use (aspirin, n=783,870; unselective NSAIDs, n=566,209, selective COX-2 inhibitors, n=17,948) compared to the Swedish background population of the same age, sex and calendar period.

Outcome measures: the risk of different gastro-intestinal cancer types expressed as standardized incidence ratios (SIR) and 95% confidence intervals (CI), taking into account concurrent proton-pump-inhibitors (PPIs) and statins usage.

Results: The SIR for gastro-intestinal cancer for aspirin-use was 1.02 (95%CI 1.00-1.04), with clearly reduced risk for long-term users (SIR=0.31, 95%CI 0.30-0.33 for 5.5-7.7 years), and stronger protective effect for low-dose aspirin (SIR=0.86, 95% CI 0.85-0.88). Users of non-selective NSAIDs showed an overall decreased risk of gastrointestinal cancer (SIR=0.79, 95%CI 0.77-0.82), in particular for cancer of the stomach, colorectum and oesophagus, and the SIRs were further decreased among long-term users. Users of selective COX-2 inhibitors showed a SIR=0.89 (95%CI 0.73-1.09) for gastrointestinal cancers. Both aspirin and unselective NSAIDs users who also

were using PPIs, had higher risks for all gastrointestinal cancer types; and lower risk if using statins.

Conclusion: Long-term use of (low-dose) aspirin and non-selective NSAIDs was associated with a decreased risk of all gastrointestinal cancer types.

Key words: gastro-intestinal cancer, chemoprevention, non-steroidal anti-inflammatory drugs, aspirin, coxibs, cancer, pharmaco-epidemiology.

Article summary: Strengths and limitations of this study

- Population-based and nationwide design based on contemporary use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) – resulting in sufficient power to assess less common types of gastrointestinal cancer, and different formulations of NSAIDs.
- Concurrent maintenance use of statins and proton pump inhibitors is assessed.
- This study is based on real-life user information because of the population-based design, which leads to inherent problems of confounding by indication and reverse causality which were taken into account in the design and analyses.
- The findings are standardized for age, sex – which are often described the major confounding factors in epidemiologic studies - and calendar time. Yet, other confounders could not be taken into account because the information was not available for the total background population.
- Exposure information is based on the Swedish Prescribed Drug Registry, which is initiated in July 2005 and has a complete nationwide coverage.

Introduction

Inflammatory processes in tumour tissue are likely to contribute to tumour progression, immunosuppression and facilitate tumour growth, and cancer susceptibility and severity may also depend on different inflammatory responses.[1] Therefore, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are among the most promising candidates for chemoprevention of cancer, in particular tumours of the gastrointestinal tract. Despite the different indications for maintenance use of aspirin and non-aspirin NSAIDs, the underlying mechanisms of these medications are similar.[2 3] NSAIDs inhibit cyclo-oxygenase (COX), an enzyme responsible for the formation of thromboxane (a lipid acting as a vasoconstrictor, which also facilitates platelet aggregation) and prostaglandins (a messenger molecule in the inflammatory pathway); yet only aspirin permanently inhibits platelet formation.[4 5] There are 2 types of NSAIDs, inhibiting both COX-1 and COX-2, or only COX-2. COX-1 is expressed in most tissues regulating many physiological processes.[6] By inhibiting prostaglandin synthesis, NSAIDs compromise gastroduodenal defence mechanisms, including reducing blood flow and mucus and bicarbonate secretion, which may lead to dyspepsia and peptic ulcers, for which proton pump inhibitors (PPIs) are often prescribed as prevention or treatment.[5 6] COX-2 is expressed at sites of inflammation, and is the actual target of NSAIDs.[6] In contrast to non-selective COX-inhibitors (i.e. aspirin and most other NSAIDs), COX-2 selective inhibitors or coxibs are also weakly acidic, and therefore avoid substantial accumulation in (and damage of) the gastric mucosa.[6] Clinical studies have shown similar anti-inflammatory effects, a lower risk of

gastrointestinal toxicity, yet a higher risk of cardiovascular morbidity for COX-2 selective inhibitors compared to nonselective COX-inhibitors.[3 7], [8] Some of the older NSAIDs are “relatively selective COX-2 inhibitors”, i.e. nabumetone, meloxicam, etodolac and nimesulide.[3]

However, epidemiological evidence to support a chemopreventive effect is still limited, mainly because large numbers are needed with a long follow-up, in particular for relatively rare cancer types. Meta-analyses have pooled the evidence of the gastrointestinal cancer preventive potential of aspirin and other NSAIDs.[9-14] A large meta-analysis[15] and another detailed scientific assessment[16] concluded that a preventive effect on colorectal cancer was especially pronounced in daily and long-term users (>5 years) in both interventional and observational studies.[15 16] Yet, the included studies used several different definitions of exposure, ranging from a single prescription of aspirin to daily use for >5 years, with too few studied reporting stratified analyses per dosage (or indication e.g. low dose anti-coagulants versus high dose analgesics) to draw reliable conclusions (although low dose has been recommended by individual studies).[15] The statistical power was too low to identify associations with many other types of (gastro-intestinal) cancer, and more, large original studies are needed to assess the potential preventive effect of other NSAIDs.[15]

The role of PPI use on the association between NSAIDs with gastrointestinal cancer is insufficiently understood yet increasingly investigated, with growing evidence of carcinogenic and other long-term side-effects of PPIs.[17-20]

The objective of this study was to assess the association of aspirin and other NSAIDs on the risk of different gastrointestinal cancer types, while also assessing the potential influence of concomitant PPI use.

Material and Methods

This nationwide Swedish population-based cohort study assessed the risk of gastrointestinal cancer in adult NSAIDs users compared to the risk in the entire Swedish background population of the corresponding sex, age and calendar year (7.1-7.6 million adults). [21] [21] [21] [21] [21] [21] [21] [21] [21] [21][21] Participants were enrolled during the study period from July 1, 2005 (the start of the Swedish Prescribed Drug Registry) to December 31, 2012. The cohort members were followed up until the occurrence of any cancer (excluding non-melanoma skin cancer), death or December 31, 2012 (i.e. the end of data collection for the Swedish Cancer Registry), whichever occurred first. Individuals with a history of any cancer were excluded, as well as individuals with a cancer diagnosis within 12 months after inclusion (to avoid reverse causation). The unique 10-digit personal identity number, assigned to each Swedish resident, was used for identification of all participants and for linkages of their individual data between registries. This study was conducted according to a detailed and a-priori established study protocol.

Data collection

The data for the present study were derived from our Chemoprevention of cancer cohort. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's

human research committee, the Regional Ethical Review Board in Stockholm, without need for informed consent (2014/1291-31/4, approved 27 AUG 2014)(see Supplement 1 and [22-24]). This data collection originates from the nationwide complete Swedish Prescribed Drug Registry, and includes all individuals residing in Sweden who have collected at least one dispensed prescription of any commonly prescribed drug between July 1, 2005 and December 31, 2014 (approximately 85% of all Swedish residents); with follow-up for cancer until December 31, 2012. This cohort has been linked to two other high-quality and complete nationwide Swedish registries, i.e. the Swedish Cancer Registry (>96% completeness of all cancers, originated in 1961),[25] and the Swedish Causes of Death Registry (>99% completeness, originated in 1952), by means of the personal identity number.

Exposures

Therapy with systemic NSAIDs was defined as at least 6 months (≥180 days) cumulative exposure during the study period. This was a cumulative exposure based on the defined daily dosage (DDD) per prescribed package, which takes into account the potency of the drug as well as the prescribed quantity. Three main types of NSAIDs were categorized based on their mechanisms of action (selective or non-selective COX inhibition) and drug class (aspirin or non-aspirin NSAIDs) with corresponding Anatomical Therapeutic Chemical classification codes (ATC): 1) aspirin (B01AC06, N02BA), 2) selective COX-2 inhibitors (coxibs, M01AH), and 3) non-selective non-aspirin NSAIDs (remaining M01A codes). Individuals with ≥180 days of exposure to 2 or 3 of these groups were excluded, so the 3 groups are mutually exclusive. Users of

combination preparations including aspirin, i.e. with corticosteroid (M01BA03), PPIs (B01AC56), statins (C10BX), as well as preparations for local (oral) use (A01AD05) were also excluded.

Additionally, the relatively selective NSAIDs, a subgroup of the non-selective NSAID users, containing meloxicam (M01AC06) and nabumetone (M01AX01), were also analysed separately. Aspirin users were also divided in 2 groups according to their ATC code (≥180 days): low dose (B01AC06), and high dose aspirin (N02BA) (those using both for ≥180 days were excluded).[26] High-dose aspirin (N02BA) and some other NSAIDs (Diclofenac, M01AB05 and Ibuprofen, M01AE01) are also available over the counter in Sweden, but they are sold in only small packages and at higher prices per dose.[26 27] Thus, we can assume that maintenance users had their doses prescribed, and were thus recorded in the present study.

Outcomes

The outcome was a first gastrointestinal cancer diagnosis recorded in the Swedish Cancer Registry according to the International Classification of Diseases (ICD) 10th edition. Gastrointestinal cancers were categorized as follows: any gastrointestinal cancer (C15-C26) or cancer of the oesophagus (C15), stomach (C16), small bowel (C17), colorectum (C18-C21), liver (C22), gallbladder or bile ducts (C23-24), or pancreas (C25). The category “other gastrointestinal cancer” (C26) was not analysed separately. Additionally, the most common histological tumour types were analysed separately: adenocarcinoma (code 096) for oesophageal, gastric, gallbladder/biliary tract, pancreas and colorectal cancer; squamous cell carcinoma (code 146) for

oesophageal cancer; hepatocellular carcinoma (code 066) for liver cancer; and carcinoid (code 086) for small bowel cancer.

Statistical analyses

The relative risks of developing gastrointestinal cancer in individuals exposed to the drugs under study were standardized using the Swedish background population of the corresponding age, sex, and calendar period. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated, while accounting for changes in age and calendar categories when calculating years of follow-up.[28] Follow-up time was counted from the dispense date of the first NSAID prescription to the date of a first cancer diagnosis, death, or the end of the study (31st December 2012), whichever occurred first. The expected incidence rates were calculated from cancer data recorded in the Swedish Cancer Registry and the age-stratified number of individuals per calendar year according to Statistics Sweden (Population Statistics). The overall SIR for gastrointestinal cancer was calculated, as well as SIRs for each anatomical location separately, including sub-analyses for the most common histological types. The analyses were also stratified for sex and age for each cancer type. Subgroup analyses were performed for high-dose and low-dose aspirin, users of relatively selective NSAIDs, NSAID use with concurrent PPI (A02BC) or statin (C10AA) use (≥180 days) if the groups were sufficiently large. To assess the effect of PPI and statins, a multivariable Poisson regression model was fitted, adjusting for age at first prescription, sex and interaction between PPI and statins, and presented as incidence rate ratios (IRR) and 95%CI. The duration of the exposures was assessed by

dividing the total cumulative dosage (sum of DDDs per package) received before the cancer diagnosis into four equally sized groups (quartiles), yet their total follow-up time was taken into account for the analyses. There were no missing data on exposures, outcomes or confounding variables. Effect estimates were only reported when at least 5 individuals developed the outcome.

Patient involvement

The Swedish patient organization for cancer of the esophagus, stomach, liver, and pancreas was involved in supporting the present study (www.palema.org). The development of the research question and outcome measures were informed by patients' priorities, experience, and preferences. The results will be disseminated to study participants by means of patient organizations. Patients are thanked in the acknowledgements.

Results

Among all 1,368,027 users of NSAIDs, there were 783,870 (57.3%) aspirin users, 566,209 (41.4%) non-selective NSAIDs users, and 17,948 (1.3%) COX-2 users (Table 1, Supplement 1). Aspirin users were more likely to be male (53.8%) and older than 70 years (54.9.2%), while non-selective NSAID users and COX-2 users were predominantly female (62.8% and 59.9%, respectively) and between 40 and 70 years of age (68.2% and 70.8%, respectively). Use of PPIs was found in 25.6%, 26.2%, and 31.2% of the aspirin users, non-selective NSAIDs users, and COX-2 users, respectively; and use of statins in 55.2%, 13.7% and 14.4%, respectively. The majority of

the population received their first prescription during the first half year of the study period (2005), 54.9% of aspirin users, and 42.5% of non-selective NSAIDs users (Supplement 2).

Aspirin

As presented in Table 1, 10.969 (1.40%) aspirin users developed some type of gastrointestinal cancer during the follow-up. The most common cancer sites were colorectal (n=6,919; 0.88%), gastric (n=1,079; 0.14%), and pancreatic (n=1,114; 0.14%). There was no association with gastrointestinal cancer based on the overall SIRs for aspirin users (SIR=1.02, 95% CI 1.00-1.04) (Table 2). Shorter duration of use (<5.5 years) seemed to be associated with an increased risk for all gastro-intestinal cancers. Yet, longer duration of aspirin use was followed by a decreased SIR for gastrointestinal cancer (SIR=0.31, 95% CI 0.30-0.33 for those with an estimated use between 5.5-7.7 years, and SIR=0.37, 95%CI 0.35-0.40 for >7.7 years) (Table 3) and long-term aspirin users had clearly decreased SIRs for each gastrointestinal cancer type (Table 3). The subgroup analyses including only the low-dosage aspirin users (N=668,305, 85.3% of the aspirin cohort) showed lower SIRs for all cancer locations, with significantly reduced risks for all locations except for oesophageal, gastric and liver cancer (Table 4).

Non-selective NSAIDs

Table 1 shows that 3,428 (0.61%) of the non-selective NSAID users developed cancer, mainly colorectal (n=2,017; 0.36%), pancreatic (n=490; 0.09%), and gastric cancers (n=260; 0.05%). Overall, there was a decreased

risk of gastrointestinal cancer (SIR=0.79, 95%CI 0.77-0.82), and also for gastric (SIR=0.70, 95% CI 0.62-0.80), colorectal (SIR=0.74, 95% CI 0.71-0.77) and oesophageal (SIR=0.75, 95% CI 0.63-0.89) cancers analysed separately (and their main histological subtypes) (Table 2). There was no evidence of decreased SIRs for the other types of gastrointestinal cancer types, although the effect sizes indicated a decreased SIR of small bowel and liver cancer. Longer duration of use of non-selective NSAIDs was associated with a decreased gastrointestinal cancer risk for all anatomical locations (Table 3).

Selective COX-2 inhibitors

Overall, 100 (0.56%) COX-2 users developed some type of gastrointestinal cancer, predominantly colorectal (n=60; 0.33%), pancreatic (n=13; 0.07%), gastric (n=7; 0.04%), and oesophageal cancers (n=7; 0.04%). There was some evidence for a decreased risk of gastrointestinal cancer overall (SIR=0.89, 95% CI 0.73-1.09), although not statistically significant. None of the sub-analyses showed strong evidence for an association (Table 4).

Relatively selective NSAIDs

Among the non-selective NSAIDs users, 7,609 individuals used relatively selective NSAIDs, of whom 74 (0.01%) developed cancer. There was no evidence for an association with any of the gastrointestinal cancer locations (Table 4).

Aspirin with PPIs or statins

Users of aspirin with concomitant use of PPIs had higher SIRs for all gastrointestinal cancers compared to those not using PPIs, with all SIRs indicating an increased risk except for gallbladder cancer (Table 5). The SIRs were especially increased for gastric cancer (SIR=1.89; 95% CI 1.73-2.06) and oesophageal cancer (SIR=1.94; 95% CI 1.71-2.20). When using Poisson regression to compare aspirin users using PPIs directly with aspirin users not using PPIs (instead of using the background population as reference), the risk was increased for all gastrointestinal cancers (IRR=1.19, 95% CI 1.11-1.26), with significantly increased risks for oesophageal, gastric, small bowel, liver and pancreatic cancer (Supplement 3).

Among aspirin users exposed to statins, the SIRs were close to unity for each anatomical location (Table 5). When aspirin users using statins were directly compared with aspirin users not using statins, risks were decreased for all gastrointestinal cancers (IRR=0.81, 95% CI 0.77-0.85), with significant decreases for all cancer locations except for colorectal and pancreatic cancer (Supplement 3).

Non-selective NSAIDs with PPIs or statins

In users of non-selective NSAIDs on therapy with PPIs, the SIRs were increased for all gastrointestinal cancer types (and again higher than among those not using PPIs), except for colorectal cancer (Table 5). When users of non-selective NSAIDs using PPIs were directly compared with those not using PPIs, risks were increased for all gastrointestinal cancers (IRR=1.61, 95% CI 1.49-1.74), and each individual cancer location except for gallbladder cancer

(Supplement 3). Among non-selective NSAIDs users using statins, the SIRs were lower than among all users of non-selective NSAIDs, and significantly reduced for oesophageal, gastric and colorectal cancer. When users of non-selective NSAIDs using statins were directly compared with those not using statins, risks were decreased for all gastrointestinal cancers (IRR=0.86, 95% CI 0.76-0.96), yet not significant for the individual cancer locations (Supplement 3).

Discussion

This study on contemporary use of NSAIDs showed a decreased risk of all types of gastrointestinal cancer among long-term users of aspirin (>5.5 years) and non-selective NSAIDs users even for shorter duration of use (>0.7 years). Long-term users of non-selective NSAIDs were at a particularly decreased risk for gastric, oesophageal, and colorectal cancers. These seemingly protective associations might be counteracted by concomitant PPI therapy, and enhanced by concomitant statin use.

The main strengths of this study are the population-based design and large sample size, including all adults residing in Sweden during the study period, which enabled separate analyses for contemporary use of different types of NSAIDs, and evaluation of less common types of gastrointestinal cancer which could not be assessed previously because of insufficient power, in particular for non-aspirin NSAIDs. Other advantages include the complete follow-up and accurate censoring for mortality. The data on the exposures (medications) and outcomes (gastrointestinal cancers) were highly accurate

due to the validity and completeness of the Swedish registries, eliminating recall bias.

Although our findings for aspirin are largely consistent with the literature, that the protective effect is only seen after 5 years, reverse causation, confounding and/or bias appear to influence the aspirin analyses because of the apparent initial increased risk of cancer among short-term users. By excluding all individuals diagnosed with cancer within a year after enrolment, and only including those with a minimal accumulated duration of use of 6 months, the risk of reverse causation should be reduced. Yet, our results indicate that those with an estimated duration shorter than 5 years have an apparent increased risk, which might be because they take aspirin because of cancer-related pain or thrombotic events – indicating confounding by indication and reverse causation among the group with the shortest exposure time, an effect which could not have been detected in intervention trials or in case-control studies with a study-design-inherent more restrictive selection of study participants.[15 29] As previous studies reported, 15-20% of cancer patients have thrombotic complications during the course of the disease (often as early manifestation of an occult malignancy),[30] yet these complications (e.g. deep venous thrombosis) are more likely to be treated with anti-coagulants than aspirin. However, when only looking at those exclusively using low-dose aspirin for ≥180 days, i.e. the platelet aggregation inhibitors, the protective effects were also visible in the overall analyses non taking into account duration, with SIR=0.86 (95%CI 0.85-0.88). This indicates that the apparent increased risks are mainly because of the small group using aspirin as

analgesic (high dose), which shows it is important to distinguish between both groups of aspirin-use. Reverse causality seems to be less of a problem for other NSAIDs users, although these may be used as analgesics.[31] Yet, individuals using NSAIDs may be at a lower a-priori risk of developing gastro-intestinal cancer, because individuals with upper gastro-intestinal symptoms are less likely to be chronic NSAIDs users due to the risk of gastro-intestinal side-effects.

Especially for aspirin users (with a high cardiovascular mortality), death is a competing risk for the development of cancer, reducing the number at risk to develop cancer. Therefore, we censored follow-up time at time of death. In this cohort the standardised mortality risks were 9.64 (95%CI 9.60-9.69) for aspirin users and 2.08 (95% CI 2.05-2.11) for non-selective non-aspirin NSAIDs users indeed showing a higher risk of death competing with the risk of cancer.

Another limitation is potential confounding, e.g. by socio-economic status, dietary factors, obesity, tobacco smoking, and alcohol consumption, which could not be taken into account since such information was not available for the total background population. However, we adjusted for age, sex and calendar period. We may have incomplete exposure ascertainment (and underestimation of duration of use) for part of our cohort since no information was available on prescriptions before July 2005 or over-the-counter use. Yet, potential long-term (protective) effects may be expected to decrease gradually yet significantly after treatment cessation, reducing the potential effect of misclassification on our results due to exposure before 2005. We used the

minimal exposure criterion of 180 days to exclude occasional users who are more likely to obtain their NSAIDs over-the-counter, so at a higher price. We did not have data on used daily dosage or duration of use, and used a proxy variable for duration based on accumulation of the average DDDs per package. This explains why some aspirin users had an estimated exposure time longer than the duration of follow-up, indicating a high daily dose. The high variability in actual and estimated administered dosage also hindered assessment of recency of use. Some previous studies subdivided aspirin use into “low dose” and “high dose” based on prescribed dosages (e.g. <75 mg/day[32] or <100 mg/day[14]), but since we did not have information on the number of prescribed pills per day, and different dosages could have been prescribed during the study period, we used the definition based on ATC coding and assessed the estimated duration of use, with the additional advantage that the low-dose aspirin was only available on prescription. This should also be a more accurate reflection of duration of use than the number of prescriptions.[9] In our study, the DDD per package could range from <5 to 500 (for other NSAIDs) or 1000 (for aspirin), which illustrates the variation between prescriptions. Since 1.4 million individuals were exposed to NSAIDs (≥180 days), i.e. one fifth of the adult population in Sweden, our results are likely to be diluted since we compared them with the total background population. Yet, despite this dilution the associations among long-term users were strongly decreased.

Compared to previous studies, this study was better powered to separately analyses different gastrointestinal cancers and types of NSAIDs.[33] The

above mentioned meta-analysis[15] identified only 2 cohort studies including over 100,000 individuals assessing colorectal cancer risk among aspirin-users.[34 35] Even our exposed groups for aspirin and non-selective NSAIDs alone were 5-7 times larger than earlier large studies. The decrease in gastrointestinal cancer risk became evident only after longer exposure, which has also been shown in previous research,[15 36] and is biologically plausible given the expected time latency for (hindering) cancer progression.

The higher risk among aspirin and other NSAID users also using PPIs should be interpreted with some caution. PPIs are often prescribed for gastroesophageal reflux and peptic ulcers, which are risk factors for oesophageal and gastric cancer, respectively. Therefore, a higher cancer risk was expected for those locations, yet not for the other gastrointestinal cancer types. PPIs can also be used to prevent peptic ulcers in users of aspirin and other NSAIDs, usually in individuals without any gastro-intestinal morbidity. Another study of our group based on the same source cohort,[24] investigated the risk of gastric cancer among PPI maintenance users, which suggested an increased risk in all indication groups for PPI (including those without gastrointestinal symptoms); which also supports a potential independent role for PPI in carcinogenesis as also suggested recently by other groups.[37 38] Together with a potential increased risk of mortality related to long-term PPI use,[39] we believe a more careful approach should be considered when prescribing PPIs to prevent gastrointestinal complications in long-term NSAIDs users. Yet, the risk for gastrointestinal complications such as bleeding should be assessed on an individual bases based on other research

investigating shorter-term effects.[40] Before considering implementing aspirin or other NSAIDs as wide-spread intervention, safety, in particular considering long-term use, needs to be considered, with previous research tending towards a “favourable benefit harm-profile” despite an excess risk of bleeding.[41]

To conclude, this large Swedish nationwide and population-based cohort study on contemporary and long-term use of NSAIDs indicates a strongly protective effect of long-term use of both (low-dose) aspirin and other non-selective NSAIDs on gastrointestinal cancer development.

Acknowledgements: We are grateful to all thousands of patients, physicians and healthcare staff members who contributed to the data collection, and to the Swedish National Board of Health and Welfare that collected the data.

Authors’ contributions: NB is the submission guarantor. NB and JL had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. NB conducted and is responsible for the data-analysis. Literature search: NB; Design of the study: both authors; Data collection and preparation for analyses: NB; Data analysis: NB; Data interpretation: both authors; Writing of first draft: NB, revised and approved by both authors.

Funding: This work was supported by SFO epidemiology (Karolinska Institutet, junior investigator award NB), Swedish Research Council (839-

2008-7496), Swedish Cancer Society (CAN 2015/460). These funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Competing interests: none

Data sharing statement: We are willing to share data upon request after ethics approval has been approved by the relevant committee and the governmental agencies that maintain the data.

References

1. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;**357**(9255):539-45 doi: 10.1016/s0140-6736(00)04046-0[published Online First: Epub Date]|.
2. Simon LS, Yocum D. New and future drug therapies for rheumatoid arthritis. Rheumatology (Oxford) 2000;**39 Suppl 1**:36-42
3. Yang M, Wang HT, Zhao M, et al. Network Meta-Analysis Comparing Relatively Selective COX-2 Inhibitors Versus Coxibs for the Prevention of NSAID-Induced Gastrointestinal Injury. Medicine 2015;**94**(40):e1592 doi: 10.1097/MD.0000000000001592[published Online First: Epub Date]|.
4. Sjodahl R. Nonsteroidal anti-inflammatory drugs and the gastrointestinal tract. Extent, mode, and dose dependence of anticancer effects. Am J Med 2001;**110**(1a):66s-69s
5. Huntjens DR, Danhof M, Della Pasqua OE. Pharmacokinetic-pharmacodynamic correlations and biomarkers in the development of COX-2 inhibitors. Rheumatology (Oxford) 2005;**44**(7):846-59 doi: 10.1093/rheumatology/keh627[published Online First: Epub Date]|.
6. Bjarnason I, Thjodleifsson B. Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs: the effect of nimesulide compared with naproxen on the human gastrointestinal tract. Rheumatology (Oxford) 1999;**38 Suppl 1**:24-32
7. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;**375**(26):2519-29 doi: 10.1056/NEJMoa1611593[published Online First: Epub Date]|.
8. Bakhriansyah M, Souverein PC, de Boer A, et al. Gastrointestinal toxicity among patients taking selective COX-2 inhibitors or conventional NSAIDs, alone or combined with proton pump inhibitors: a case-control study. Pharmacoepidemiol Drug Saf 2017 doi: 10.1002/pds.4183[published Online First: Epub Date]|.

9. Capurso G, Schunemann HJ, Terrenato I, et al. Meta-analysis: the use of non-steroidal anti-inflammatory drugs and pancreatic cancer risk for different exposure categories. Aliment Pharmacol Ther 2007;**26**(8):1089-99 doi: 10.1111/j.1365-2036.2007.03495.x[published Online First: Epub Date]|.
10. Tian W, Zhao Y, Liu S, et al. Meta-analysis on the relationship between nonsteroidal anti-inflammatory drug use and gastric cancer. Eur J Cancer Prev 2010;**19**(4):288-98 doi: 10.1097/CEJ.0b013e328339648c[published Online First: Epub Date]|.
11. Yang P, Zhou Y, Chen B, et al. Aspirin use and the risk of gastric cancer: a meta-analysis. Dig Dis Sci 2010;**55**(6):1533-9 doi: 10.1007/s10620-009-0915-0[published Online First: Epub Date]|.
12. Ye X, Fu J, Yang Y, et al. Dose-risk and duration-risk relationships between aspirin and colorectal cancer: a meta-analysis of published cohort studies. PLoS One 2013;**8**(2):e57578 doi: 10.1371/journal.pone.0057578[published Online First: Epub Date]|.
13. Ye X, Fu J, Yang Y, et al. Frequency-risk and duration-risk relationships between aspirin use and gastric cancer: a systematic review and meta-analysis. PLoS One 2013;**8**(7):e71522 doi: 10.1371/journal.pone.0071522[published Online First: Epub Date]|.
14. Cui XJ, He Q, Zhang JM, et al. High-dose aspirin consumption contributes to decreased risk for pancreatic cancer in a systematic review and meta-analysis. Pancreas 2014;**43**(1):135-40 doi: 10.1097/MPA.0b013e3182a8d41f[published Online First: Epub Date]|.
15. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 2012;**13**(5):518-27 doi: 10.1016/S1470-2045(12)70112-2[published Online First: Epub Date]|.
16. Sutcliffe P, Connock M, Gurung T, et al. Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews. Health Technol Assess 2013;**17**(43):1-253 doi: 10.3310/hta17430[published Online First: Epub Date]|.

17. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. Gut 2016;**65**(5):740-8 doi: 10.1136/gutjnl-2015-310376[published Online First: Epub Date]|.
18. Alsalahi O, Dobrian AD. Proton Pump Inhibitors: The Culprit for Barrett's Esophagus? Front Oncol 2014;**4**:373 doi: 10.3389/fonc.2014.00373[published Online First: Epub Date]|.
19. Kia L, Kahrilas PJ. Therapy: Risks associated with chronic PPI use - signal or noise? Nat Rev Gastroenterol Hepatol 2016 doi: 10.1038/nrgastro.2016.44[published Online First: Epub Date]|.
20. Poulsen AH, Christensen S, McLaughlin JK, et al. Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. Br J Cancer 2009;**100**(9):1503-7 doi: 10.1038/sj.bjc.6605024[published Online First: Epub Date]|.
21. Statistics Sweden - Statistical Database Population Statistics (accessed 06 April 2016) http://www.statistikdatabasen.scb.se/. Secondary Statistics Sweden - Statistical Database Population Statistics (accessed 06 April 2016) http://www.statistikdatabasen.scb.se/. http://www.statistikdatabasen.scb.se/.
22. Sadr-Azodi O, Konings P, Brusselaers N. Menopausal hormone therapy and pancreatic cancer risk in women: a population-based matched cohort study. United European gastroenterology journal 2017;**5**(8):1123-28 doi: 10.1177/2050640617702060[published Online First: Epub Date]|.
23. Ma Y, Brusselaers N. Maintenance use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) and prostate cancer risk. Prostate cancer and prostatic diseases 2017 doi: 10.1038/s41391-017-0021-x[published Online First: Epub Date]|.
24. Brusselaers N, Wahlin K, Engstrand L, et al. Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden. BMJ Open 2017;**7**(10):e017739 doi: 10.1136/bmjopen-2017-017739[published Online First: Epub Date]|.

25. Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 2009;**48**(1):27-33 doi: 902131375 [pii]
10.1080/02841860802247664[published Online First: Epub Date]|.
26. FASS (Farmacevtiska specialiteter i Sverige/ Farmaceutical specialities in Sweden), 2015.
27. Läkemedelsverket (Medical Products Agency): Over-the-counter (OTC). Secondary Läkemedelsverket (Medical Products Agency): Over-the-counter (OTC) 2016. https://lakemedelsverket.se/english/product/Medicinal-products/OTC/.
28. Breslow N, Day N. *Statistical Methods in Cancer Research: The design and analysis of cohort studies*. Lyon, 1987.
29. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 2010;**376**(9754):1741-50 doi: 10.1016/S0140-6736(10)61543-7[published Online First: Epub Date]|.
30. Kyriazi V, Theodoulou E. Assessing the risk and prognosis of thrombotic complications in cancer patients. Arch Pathol Lab Med 2013;**137**(9):1286-95 doi: 10.5858/arpa.2012-0490-RA[published Online First: Epub Date]|.
31. Mercadante S. The use of anti-inflammatory drugs in cancer pain. Cancer Treat Rev 2001;**27**(1):51-61 doi: 10.1053/ctrv.2000.0192[published Online First: Epub Date]|.
32. Din FV, Theodoratou E, Farrington SM, et al. Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. Gut 2010;**59**(12):1670-9 doi: 10.1136/gut.2009.203000[published Online First: Epub Date]|.
33. Bosetti C, Rosato V, Gallus S, et al. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol 2012;**23**(6):1403-15 doi: 10.1093/annonc/mds113[published Online First: Epub Date]|.
34. Jacobs EJ, Thun MJ, Bain EB, et al. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst 2007;**99**(8):608-15 doi: 10.1093/jnci/djk132[published Online First: Epub Date]|.

35. Smalley W, Ray WA, Daugherty J, et al. Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. Arch Intern Med 1999;**159**(2):161-6
36. Cao Y, Nishihara R, Wu K, et al. Population-wide Impact of Long-term Use of Aspirin and the Risk for Cancer. JAMA Oncol 2016;**2**(6):762-9 doi: 10.1001/jamaoncol.2015.6396[published Online First: Epub Date]|.
37. Cheung KS, Chan EW, Wong AYS, et al. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut 2018;**67**(1):28-35 doi: 10.1136/gutjnl-2017-314605[published Online First: Epub Date]|.
38. Niikura R, Hayakawa Y, Hirata Y, et al. Long-term proton pump inhibitor use is a risk factor of gastric cancer after treatment for Helicobacter pylori: a retrospective cohort analysis. Gut 2017 doi: 10.1136/gutjnl-2017-315710[published Online First: Epub Date]|.
39. Xie Y, Bowe B, Li T, et al. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. BMJ Open 2017;**7**(6):e015735 doi: 10.1136/bmjopen-2016-015735[published Online First: Epub Date]|.
40. Li L, Geraghty OC, Mehta Z, et al. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017;**390**(10093):490-99 doi: 10.1016/s0140-6736(17)30770-5[published Online First: Epub Date]|.
41. Cuzick J, Thorat MA, Bosetti C, et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol 2015;**26**(1):47-57 doi: 10.1093/annonc/mdu225[published Online First: Epub Date]|.

Table 1: Characteristics of the study cohort on therapy with aspirin, selective cyclo-oxygenase-2 (COX-2) inhibitors, and non-selective non-steroidal anti-inflammatory drug (NSAIDs).

	Aspirin only	Non-selective non-aspirin NSAIDs	Selective COX-2 inhibitors
	Number (%)	*Number (%)*	*Number (%)*
Total	783,870	566,209	17,948
Sex			
Men	421,609 (53.8)	210,705 (37.2)	7,201 (40.1)
Women	362,261 (46.2)	355,504 (62.8)	10,747 (59.9)
Age at first prescription			
<40 years	12,189 (1.6)	110,592 (19.5)	2,720 (15.2)
40-49 years	32,743 (4.2)	125,977 (22.3)	3,849 (21.5)
50-59 years	108,683 (13.9)	146,981 (26.0)	4,941 (27.5)
60-69 years	200,154 (25.5)	112,682 (19.9)	3,914 (21.8)
≥70 years	430,101 (54.9)	69,977 (12.4)	2,524 (14.1)
Calendar period at first prescription			
2005-2006	557,023 (71.1)	387,443 (68.4)	10,393 (57.9)
2007-2009	156,790 (20.0)	145,208 (25.7)	5,500 (30.6)
2010-2012	70,057 (8.9)	33,558 (5.9)	2,055(11.5)
Proton pump inhibitors use (≥180 days)			
yes	200,828 (25.6)	148,586 (26.2)	5,602 (31.2)
no	583,042 (74.4)	417,623 (73.8)	12,346 (68.8)
Statins use (≥180 days)			
yes	432,996 (55.2)	77,514 (13.7)	2,589 (14.4)
no	350,874 (44.8)	488,695 (86.3)	15,359 (85.6)
Gastrointestinal cancer	10,969 (1.40)	3,428 (0.61)	100 (0.56)
Oesophageal cancer	539 (0.07)	134 (0.02)	7 (0.04)
Adenocarcinoma	319 (0.04)	75 (0.01)	4 (0.02)
Squamous cell carcinoma	203 (0.03)	50 (0.01)	2 (0.01)
Gastric cancer	1,079 (0.14)	260 (0.05)	7 (0.04)
Adenocarcinoma	949 (0.12)	212 (0.04)	3 (0.02)
Small bowel cancer	253 (0.03)	94 (0.02)	5 (0.03)
Carcinoid	122 (0.02)	43 (0.01)	2 (0.01)
Colorectal cancer	6,919 (0.88)	2,017 (0.36)	60 (0.33)
Adenocarcinoma	6,608 (0.84)	1,887 (0.33)	59 (0.33)
Liver cancer	645 (0.08)	232 (0.04)	3 (0.02)
Hepatocellular carcinoma	358 (0.05)	100 (0.02)	1 (0.01)
Gallbladder and biliary tract cancer	385 (0.05)	190 (0.03)	5 (0.03)
Adenocarcinoma	288 (0.04)	149 (0.03)	2 (0.01)
Pancreatic cancer	1,114 (0.14)	490 (0.09)	13 (0.07)
Adenocarcinoma	835 (0.11)	402 (0.07)	11 (0.06)

Other gastrointestinal cancer	35 (0.00)	11 (0.00)	0 (0.00)
Duration of follow-up in person-years			
Total	3,776,237	3,376,275	82,733
Mean (standard deviation)	4.82 (2.40)	5.96 (1.67)	4.61 (2.21)

Table 2: The risk of different types of gastrointestinal cancer (and the major histological subtype) among users of aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), expressed as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) and stratified by age and sex.

	Aspirin users (n=783,870)		Non-selective non-aspirin NSAIDs users (n=566,209)	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
Gastrointestinal cancer	**10,969**	**1.02 (1.00-1.04)**	**3,428**	**0.79 (0.77-0.82)**
Men	6,659	1.24 (1.21-1.27)	1,390	0.78 (0.74-0.82)
Women	4,310	0.99 (0.96-1.02)	2,038	0.81 (0.77-0.84)
18-39 years	3	-	14	0.59 (0.32-0.99)
40-49 years	20	0.70 (0.43-1.08)	116	0.67 (0.55-0.81)
50-59 years	408	1.13 (1.03-1.25)	423	0.61 (0.55-0.67)
60-69 years	2,286	1.13 (1.08-1.18)	1,074	0.71 (0.67-0.75)
≥70 years	8,252	0.99 (0.97-1.01)	1,801	0.94 (0.90-0.98)
Oesophageal cancer	**539**	**1.10 (1.01-1.19)**	**134**	**0.75 (0.63-0.89)**
Adenocarcinoma	319	1.17 (1.04-1.30)	75	0.81 (0.64-1.01)
Squamous cell carcinoma	203	1.06 (0.92-1.22)	50	0.66 (0.49-0.87)
Men	415	1.09 (0.99-1.20)	90	0.88 (0.63-0.97)
Women	124	1.12 (0.93-1.33)	44	0.68 (0.49-0.91)
18-39 years	0	-	0	-
40-49 years	1	-	5	0.87 (0.28-2.03)
50-59 years	21	0.99 (0.61-1.51)	18	0.58 (0.34-0.92)
60-69 years	164	1.35 (1.15-1.57)	47	0.65 (0.48-0.86)
≥70 years	353	1.02 (0.92-1.13)	64	0.92 (0.71-1.18)
Gastric cancer	**1,079**	**1.08 (1.01-1.14)**	**260**	**0.70 (0.62-0.80)**
Adenocarcinoma	949	1.07 (1.00-1.14)	212	0.66 (0.58-0.76)
Men	714	1.08 (1.00-1.16)	128	0.72 (0.60-0.85)
Women	365	1.08 (0.97-1.19)	132	0.69 (0.58-0.82)
18-39 years	0	-	1	-
40-49 years	3	-	13	0.71 (0.38-1.22)
50-59 years	51	1.48 (1.10-1.94)	37	0.61 (0.43-0.85)
60-69 years	208	1.20 (1.04-1.37)	73	0.61 (0.48-0.77)
≥70 years	817	1.03 (0.96-1.11)	136	0.81 (0.68-0.95)
Small bowel cancer	**253**	**1.05 (0.93-1.19)**	**94**	**0.84 (0.68-1.02)**
Carcinoid	122	1.11 (0.92-1.32)	43	0.84 (0.61-1.13)
Men	150	1.05 (0.89-1.23)	34	0.72 (0.50-1.00)
Women	103	1.06 (0.86-1.28)	60	0.93 (0.71-1.19)
18-39 years	0	-	1	-
40-49 years	1	-	3	-
50-59 years	18	1.53 (0.91-2.41)	18	0.77 (0.46-1.22)

60-69 years	64	1.16 (0.89-1.48)	33	0.81 (0.56-1.14)
≥70 years	170	0.99 (0.85-1.15)	39	0.98 (0.69-1.34)
Colorectal cancer	**6,919**	**1.00 (0.98-1.03)**	**2,017**	**0.74 (0.71-0.77)**
Adenocarcinoma	6,608	1.00 (0.80-1.03)	1,887	0.74 (0.70-0.77)
Men	4,105	1.03 (1.00-1.06)	793	0.73 (0.68-0.79)
Women	2,814	0.97 (0.93-1.00)	1,224	0.74 (0.70-0.78)
18-39 years	2	-	10	0.61 (0.29-1.13)
40-49 years	9	0.52 (0.24-0.98)	51	0.47 (0.35-0.62)
50-59 years	241	1.16 (1.02-1.31)	232	0.55 (0.48-0.63)
60-69 years	1,268	1.05 (0.99-1.11)	600	0.66 (0.60-0.71)
≥70 years	5,399	0.99 (0.96-1.02)	1,124	0.88 (0.83-0.94)
Liver cancer	**645**	**1.11 (1.03-1.20)**	**232**	**0.96 (0.84-1.09)**
Hepatocellular carcinoma	358	1.13 (1.02-1.25)	100	0.83 (0.77-1.01)
Men	449	1.12 (1.02-1.23)	130	1.00 (0.84-1.19)
Women	196	1.09 (0.94-1.26)	102	0.91 (0.74-1.10)
18-39 years	0	-	3	-
40-49 years	4	-	10	0.95 (0.46-1.75)
50-59 years	32	1.04 (0.71-1.47)	44	0.90 (0.65-1.21)
60-69 years	182	1.36 (1.17-1.57)	90	0.99 (0.79-1.21)
≥70 years	427	1.03 (0.94-1.14)	85	0.95 (0.76-1.17)
Gallbladder and biliary tract cancer	**385**	**0.92 (0.83-1.01)**	**190**	**1.03 (0.89-1.19)**
Adenocarcinoma	288	0.93 (0.82-1.04)	149	1.07 (0.90-1.25)
Men	181	1.00 (0.86-1.15)	50	0.98 (0.73-1.29)
Women	204	0.85 (0.74-0.80)	140	1.05 (0.88-1.24)
18-39 years	0	-	1	-
40-49 years	0	-	7	0.97 (0.39-2.00)
50-59 years	6	0.52 (.19-1.13)	12	0.46 (0.24-0.80)
60-69 years	91	1.31 (1.05-1.60)	63	1.00 (0.77-1.28)
≥70 years	288	0.85 (0.76-0.96)	107	1.23 (1.00-1.48)
Pancreatic cancer	**1,114**	**1.04 (0.98-1.11)**	**490**	**1.00 (0.92-1.10)**
Adenocarcinoma	835	1.00 (0.93-1.07)	402	1.02 (0.92-1.13)
Men	629	1.07 (0.99-1.16)	163	0.89 (0.76-1.03)
Women	485	1.01 (0.92-1.11)	327	1.08 (0.96-1.20)
18-39 years	1	-	1	-
40-49 years	3	-	26	1.65 (1.08-2.42)
50-59 years	37	0.91 (0.64-1.25)	68	0.86 (0.67-1.09)
60-69 years	307	1.19 (1.06-1.33)	174	0.85 (0.73-0.99)
≥70 years	766	1.00 (0.93-1.07)	221	1.18 (1.03-1.35)

Table 3: The risk of gastrointestinal cancer among aspirin and non-aspirin non-steroidal anti-inflammatory drug (NSAID) users, by estimated duration of use, expressed as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs).

	Aspirin only (n=783,870)			Non-selective non-aspirin NSAIDs (n=566,209)		
	Categories (quartiles)	*Number of cases*	*SIRs (95% CI)*	*Categories (quartiles)*	*Number of cases*	*SIRs (95% CI)*
Gastrointestinal cancer						
	0.5-2.5 years	4,158	2.77 (2.69-2.85)	*0.5-0.7 years*	865	1.00 (0.93-1.06)
	2.5-5.5 years	4,532	1.83 (1.77-1.88)	*0.7-1.1 years*	832	0.92 (0.86-0.98)
	5.5-7.7 years	1,310	0.31 (0.30-0.33)	*1.1-2.1 years*	977	0.86 (0.80-0.91)
	>7.7 years	969	0.37 (0.35-0.40)	*>2.1 years*	754	0.54 (0.50-0.58)
Oesophageal cancer						
	0.5-2.5 years	204	2.91 (2.52-3.33)	*0.5-0.7 years*	35	0.93 (0.65-1.29)
	2.5-5.5 years	216	1.83 (1.60-2.09)	*0.7-1.1 years*	32	0.84 (0.57-1.18)
	5.5-7.7 years	61	0.31 (0.24-0.40)	*1.1-2.1 years*	43	0.91 (0.66-1.23)
	>7.7 years	58	0.56 (0.42-0.72)	*>2.1 years*	23	0.41 (0.26-0.61)
Gastric cancer						
	0.5-2.5 years	61	2.89 (2.62-3.19)	*0.5-0.7 years*	55	0.73 (0.55-0.95)
	2.5-5.5 years	466	2.00 (1.82-2.19)	*0.7-1.1 years*	61	0.78 (0.60-1.01)
	5.5-7.7 years	99	0.26 (0.21-0.31)	*1.1-2.1 years*	80	0.82 (0.65-1.02)
	>7.7 years	110	0.45 (0.37-0.55)	*>2.1 years*	64	0.54 (0.42-0.69)
Small bowel cancer						
	0.5-2.5 years	96	2.78 (2.25-3.39)	*0.5-0.7 years*	22	0.94 (0.59-1.43)
	2.5-5.5 years	109	1.94 (1.59-2.33)	*0.7-1.1 years*	20	0.83 (0.51-1.29)
	5.5-7.7 years	26	0.28 (0.18-0.41)	*1.1-2.1 years*	25	0.85 (0.55-1.25)
	>7.7 years	22	0.39 (0.25-0.60)	*>2.1 years*	27	0.76 (0.50-1.11)
Colorectal cancer						
	0.5-2.5 years	2,658	2.78 (2.67-2.88)	*0.5-0.7 years*	540	0.99 (0.91-1.08)
	2.5-5.5 years	2,844	1.79 (1.73-1.86)	*0.7-1.1 years*	489	0.86 (0.78-0.94)

	5.5-7.7 years	813	0.31 (0.29-0.33)	*1.1-2.1 years*	565	0.78 (0.72-0.85)
	>7.7 years	604	0.36 (0.33-0.39)	*>2.1 years*	423	0.47 (0.43-0.52)
Liver cancer						
	0.5-2.5 years	222	2.63 (2.30-3.00)	*0.5-0.7 years*	63	1.23 (0.95-1.57)
	2.5-5.5 years	272	1.96 (1.74-2.21)	*0.7-1.1 years*	53	1.02 (0.76-1.33)
	5.5-7.7 years	100	0.44 (0.35-0.53)	*1.1-2.1 years*	70	1.10 (0.86-1.39)
	>7.7 years	51	0.40 (0.30-0.53)	*>2.1 years*	46	0.61 (0.45-0.81)
Gallbladder and biliary tract cancer						
	0.5-2.5 years	137	2.36 (1.98-2.79)	*0.5-0.7 years*	42	1.17 (0.85-1.58)
	2.5-5.5 years	143	1.52 (1.28-1.79)	*0.7-1.1 years*	51	1.34 (1.00-1.76)
	5.5-7.7 years	61	0.39 (0.30-.50)	*1.1-2.1 years*	52	1.06 (0.79-1.39)
	>7.7 years	44	0.40 (0.29-0.53)	*>2.1 years*	45	0.73 (0.53-0.98)
Pancreatic cancer						
	0.5-2.5 years	424	2.79 (2.53-3.06)	*0.5-0.7 years*	107	1.09 (0.90-1.32)
	2.5-5.5 years	467	1.87 (1.71-2.06)	*0.7-1.1 years*	123	1.20 (1.00-1.43)
	5.5-7.7 years	149	0.36 (0.30-0.42)	*1.1-2.1 years*	136	1.05 (0.88-1.25)
	>7.7 years	74	0.28 (0.23-0.37)	*>2.1 years*	124	0.78 (0.65-0.93)

Table 4: The risk of gastrointestinal cancer among maintenance users of cyclo-oxygenase-2 (COX-2) selective and relatively selective non-steroidal anti-inflammatory drugs (NSAIDs), and low-dose aspirin users, presented as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs).

	COX-2 selective NSAIDs maintenance users (n=17,948)		Relatively selective NSAIDs maintenance users (n=7,609)		Low-dose aspirin (n=668,305)	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
Gastrointestinal cancer	100	0.89 (0.73-1.09)	74	0.97 (0.76-1.21)	9,996	0.86 (0.85-0.88)
Oesophageal cancer	7	1.49 (0.60-3.07)	1	-	493	0.99 (0.91-1.08)
Gastric cancer	7	0.74 (0.30-1.52)	4	-	986	0.94 (0.88-1.00)
Small bowel cancer	5	1.72 (0.55-4.00)	3	-	224	0.84 (0.74-0.96)
Colorectal cancer	60	0.85 (0.65-1.09)	50	1.02 (0.76-1.35)	6,338	0.85 (0.83-0.88)
Liver cancer	3	-	3	-	592	0.97 (0.89-1.05)
Gallbladder and biliary tract cancer	5	1.05 (0.34-2.44)	3	-	344	0.74 (0.66-0.82)
Pancreatic cancer	13	1.02 (0.54-1.74)	10	1.15 (0.55-2.12)	990	0.80 (0.75-0.85)

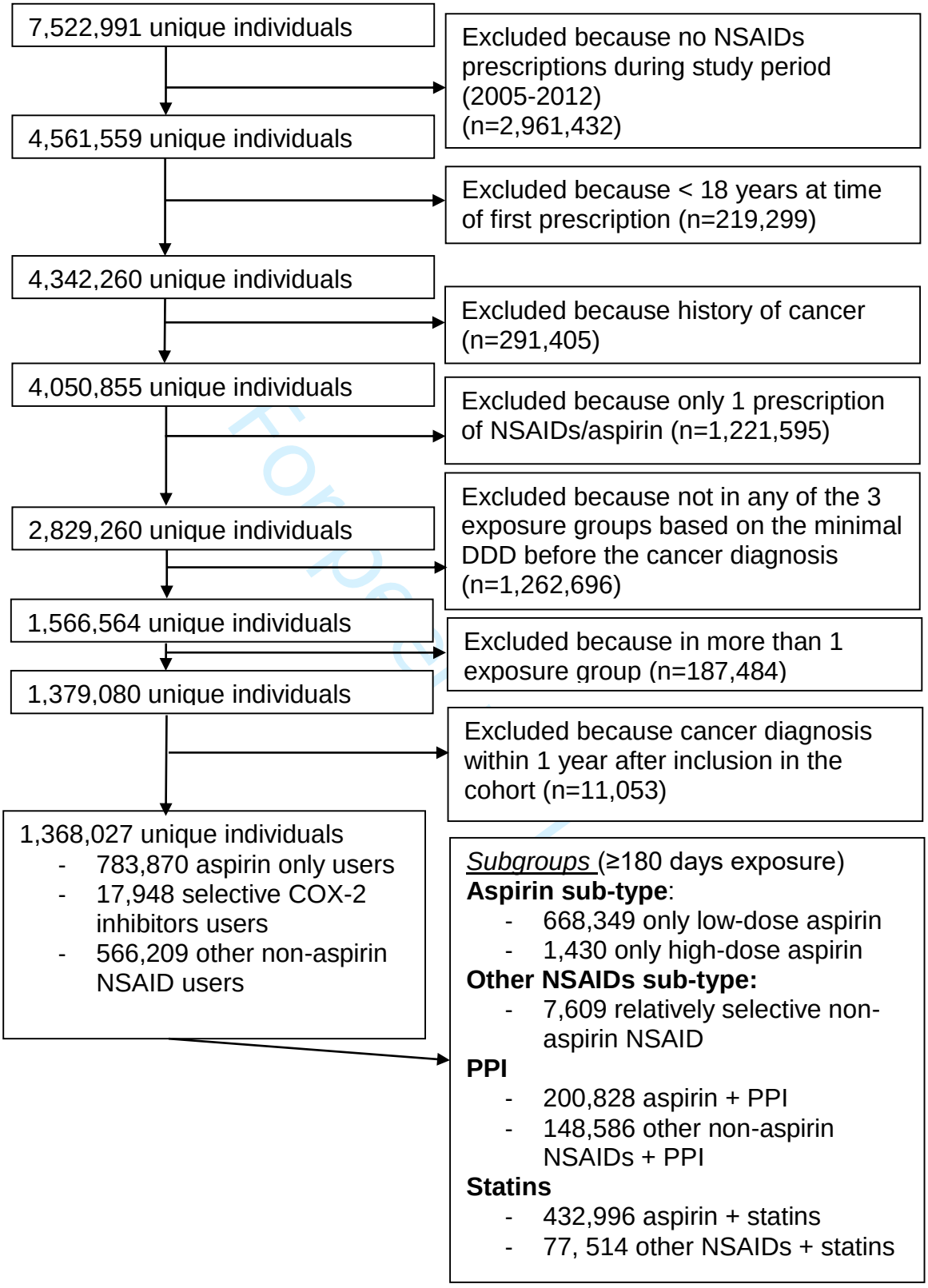
Table 5: The risk of gastrointestinal cancer among aspirin and non-selective non-aspirin non-steroidal anti-inflammatory drug (NSAID) users, stratified by additional use of proton pump inhibitors (PPIs) or statins compared to the total Swedish background population, expressed as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs).

	Aspirin users (n=783,870)		Aspirin with PPI (n=200,828)		Aspirin with statins (n=432,996)	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
All gastrointestinal cancer	10,969	1.02 (1.00-1.04)	3,617	1.25 (1.21-2.29)	6,210	0.99 (0.96-1.01)
Oesophageal cancer	539	1.10 (1.01-1.19)	247	1.94 (1.71-2.20)	299	0.98 (0.87-1.09)
Gastric cancer	1,079	1.08 (1.01-1.14)	509	1.89 (1.73-2.06)	619	1.05 (0.98-1.13)
Small bowel cancer	253	1.05 (0.93-1.19)	107	1.67 (1.37-2.01)	139	0.97 (0.81-1.14)
Colorectal cancer	6,919	1.00 (0.98-1.03)	2,004	1.07 (1.02-1.12)	3,893	0.97 (0.94-1.00)
Liver cancer	645	1.11 (1.03-1.20)	231	1.52 (1.33-1.73)	351	0.99 (0.89-1.10)
Gallbladder and biliary tract cancer	385	0.92 (0.83-1.01)	117	1.00 (0.82-1.19)	212	0.90 (0.78-1.03)
Pancreatic cancer	1,114	1.04 (0.98-1.11)	391	1.36 (1.23-1.50)	678	1.07 (0.99-2.15)

	Non-aspirin NSAIDs users (n=567,569)		Non-selective non-aspirin with PPI (n=148,586)		Non-selective non-aspirin with statins (n=77,514)	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
All gastrointestinal cancer	3,428	0.79 (0.77-0.82)	1,360	1.08 (1.02-1.13)	625	0.71 (0.65-0.76)
Oesophageal cancer	134	0.75 (0.63-0.89)	67	1.36 (1.05-1.73)	24	0.64 (0.41-0.95)
Gastric cancer	260	0.70 (0.62-0.80)	156	1.47 (1.25-1.72)	44	0.58 (0.42-0.78)
Small bowel cancer	94	0.84 (0.68-1.02)	45	1.39 (1.02-1.87)	14	0.64 (0.35-1.07)
Colorectal cancer	2,017	0.74 (0.71-0.77)	694	0.86 (0.80-0.93)	380	0.68 (0.61-0.75)
Liver cancer	232	0.96 (0.84-1.09)	102	1.51 (1.23-1.83)	38	0.78 (0.55-1.07)
Gallbladder and biliary tract cancer	190	1.03 (0.89-1.19)	68	1.21 (0.94-1.53)	29	0.76 (0.51-1.10)
Pancreatic cancer	490	1.00 (0.92-1.10)	222	1.55 (1.35-1.76)	93	0.92 (0.75-1.13)

Online Supplement 1

Description of original cohort, the “Chemoprevention of Cancer” cohort, and flow-chart describing the selection of the study cohort.



Abbreviations: COX, cyclooxygenase; DDD, defined daily dosage; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors

This cohort included all individuals residing in Sweden who received at least one dispensed prescription of one of the following commonly prescribed drugs between July 1, 2005 and December 31, 2014 (with corresponding ATC codes) with follow-up for cancer until December 2012: sex hormones (G03), drugs for peptic ulcers and gastro-esophageal reflux disease (A02B), acetylsalicylic acid (B01AC06, N02BA), non-steroidal anti-inflammatory drugs (M01A), HMG CoA reductase inhibitors (C10AA), drugs affecting bone structure and mineralization, (M05B), and antibiotics (J01AA, J01CA04, J01FA, J01MA, J01XD, J01XE, J04AB04). This cohort included approximately 85% of all Swedish residents, with especially high coverage of adults.

Supplement 2: Year of first prescription among aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) users during the study period.

	Aspirin	Non-aspirin NSAIDs
	N (%)	*N (%)*
2005	430,391 (54.9)	240,848 (42.5)
2006	79,356 (10.1)	143,805 (25.4)
2007	60,071 (7.7)	71,053 (12.6)
2008	55,527 (7.1)	46,013 (8.1)
2009	49,885 (6.4)	29,814 (5.3)
2010	43,290 (5.5)	18,957 (3.4)
2011	38,415 (4.9)	11,736 (2.1)
2012	26,935 (3.4)	3,983 (0.7)
Total	783,87	566,209

Supplement 3: The risk of gastrointestinal cancer among aspirin and non-selective non-aspirin non-steroidal anti-inflammatory drug (NSAID) users comparing users with non-users of additional proton pump inhibitors (PPI) or statins, calculated with Poisson Regression models and expressed as incidence rate ratios (IRR) and 95% confidence intervals (CIs).

	Aspirin with PPI vs. without	Aspirin with statin vs. without	Non-selective non-aspirin NSAIDs with PPI vs. without	Non-selective non-aspirin NSAIDs with statins vs. without
	IRR (95% CI)	*IRR (95% CI)*	*IRR (95% CI)*	*IRR (95% CI)*
All gastrointestinal cancer	1.19 (1.11-1.26)	0.81 (0.77-0.85)	1.61 (1.49-1.74)	0.86 (0.76-0.96)
Oesophageal cancer	2.16 (1.67-2.80)	0.59 (0.47-0.75)	2.58 (1.77-3.75)	0.65 (0.32-1.31)
Gastric cancer	2.26 (1.88-2.71)	0.81 (0.69-0.96)	3.68 (2.80-4.83)	0.62 (0.34-1.11)
Small bowel cancer	1.65 (1.12-2.42)	0.65 (0.47-0.90)	2.20 (1.41-3.42)	0.62 (0.26-1.47)
Colorectal cancer	0.98 (0.90-1.06)	0.85 (0.80-1.90)	1.30 (1.17-1.44)	0.94 (0.81-1.08)
Liver cancer	1.56 (1.23-1.99)	0.64 (0.53-0.78)	2.12 (1.59-2.82)	0.79 (0.49-1.27)
Gallbladder and biliary tract cancer	0.70 (0.49-1.02)	0.67 (0.52-0.86)	1.28 (0.92-1.77)	0.67 (0.40-1.11)
Pancreatic cancer	1.32 (1.08-1.62)	0.90 (0.77-1.04)	1.88 (1.54-2.30)	0.78 (0.55-1.09)

Adjusted for age at first prescription, sex, and interaction between PPI and statins

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

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p 1 & 3 (abstract & title)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p 5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	p 6
Methods			
Study design	4	Present key elements of study design early in the paper	p 7-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p 7-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	p 7-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p 7-10 + appendix
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	p 7-10
Bias	9	Describe any efforts to address potential sources of bias	p 7-10
Study size	10	Explain how the study size was arrived at	Fig 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p 7-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p 9-10
		(*b*) Describe any methods used to examine subgroups and interactions	p 9-10
		(*c*) Explain how missing data were addressed	p 9-10
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
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	Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p 11, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 1-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	Tables 2-4

		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	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p 11-13, appendix
Discussion			
Key results	18	Summarise key results with reference to study objectives	p 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	p 14-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p 14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	p 14-17
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	p 3, p 17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Maintenance use of non-steroidal anti-inflammatory drugs and risk of gastrointestinal cancer in a nationwide population-based cohort study in Sweden

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-021869.R1
Article Type:	Research
Date Submitted by the Author:	06-Apr-2018
Complete List of Authors:	Brusselaers, Nele; Karolinska Institutet, Molecular medicine and Surgery Lagergren, Jesper; Karolinska Institutet, Department of Molecular medicine and Surgery; King's College London, Division of Cancer Studies
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Oncology, Pharmacology and therapeutics
Keywords:	Gastrointestinal tumours < GASTROENTEROLOGY, chemoprevention, non-steroidal antiinflammatory drugs, aspirin, coxibs, cancer

Maintenance use of non-steroidal anti-inflammatory drugs and risk of gastrointestinal cancer in a nationwide population-based cohort study in Sweden.

Running title: NSAIDs and gastrointestinal cancer prevention

Authors: Nele BRUSSELAERS[1,2], MD MSc PhD, Jesper LAGERGREN[3,4], MD PhD.

Affiliations:

[1] Centre for Translational Microbiome Research, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Karolinska Hospital, Stockholm, Sweden

[2] Science for Life Laboratory (SciLifeLab), Stockholm, Sweden

[3] Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

[4] Division of Cancer Studies, King's College London, United Kingdom.

Correspondence and requests for reprints: Dr. Nele Brusselaers, Centre for Translational Microbiome Research, Department of Microbiology, Tumor and Cell biology, Karolinska Institutet, Nobelsvag16, 171 77 Stockholm, Sweden.
E-mail: Nele.Brusselaers@ki.se, Tel: +46 8 524 853 08
***Email addresses authors*:** nele.brusselaers@ki.se; jesper.lagergren@ki.se

Word count*: 3,743 words; Tables: 4, Figures: 0; supplement: 4*

Structured summary (228 words)

Objectives: Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are potential candidates for chemoprevention of gastrointestinal cancer. We aimed to assess the association between contemporary NSAID use (≥180 days) and gastrointestinal cancer.

Design: Nationwide Swedish population-based cohort study (2005-2012,

Setting: Sweden

Participants: All adults exposed to maintenance NSAIDs use (aspirin, n=783,870; unselective NSAIDs, n=566,209, selective COX-2 inhibitors, n=17,948) compared to the Swedish background population of the same age, sex and calendar period.

Outcome measures: the risk of different gastro-intestinal cancer types expressed as standardized incidence ratios (SIR) and 95% confidence intervals (CI), taking into account concurrent proton-pump-inhibitors (PPIs) and statins usage.

Results: The SIR for gastro-intestinal cancer for aspirin-use was 1.02 (95%CI 1.00-1.04), with clearly reduced risk for long-term users (SIR=0.31, 95%CI 0.30-0.33 for 5.5-7.7 years), and stronger protective effect for low-dose aspirin (SIR=0.86, 95% CI 0.85-0.88). Users of non-selective NSAIDs showed an overall decreased risk of gastrointestinal cancer (SIR=0.79, 95%CI 0.77-0.82), in particular for cancer of the stomach, colorectum and oesophagus, and the SIRs were further decreased among long-term users. Users of selective COX-2 inhibitors showed a SIR=0.89 (95%CI 0.73-1.09) for gastrointestinal cancers. Both aspirin and unselective NSAIDs users who also

were using PPIs, had higher risks for all gastrointestinal cancer types; and lower risk if using statins.

Conclusion: Long-term use of (low-dose) aspirin and non-selective NSAIDs was associated with a decreased risk of all gastrointestinal cancer types.

Key words: gastro-intestinal cancer, chemoprevention, non-steroidal anti-inflammatory drugs, aspirin, coxibs, cancer, pharmaco-epidemiology.

Article summary: Strengths and limitations of this study

- Population-based and nationwide design based on contemporary use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) – resulting in sufficient power to assess less common types of gastrointestinal cancer, and different formulations of NSAIDs.
- Concurrent maintenance use of statins and proton pump inhibitors is assessed.
- This study is based on real-life user information because of the population-based design, which leads to inherent problems of confounding by indication and reverse causality which were taken into account in the design and analyses.
- The findings are standardized for age, sex – which are often described as the major confounding factors in epidemiologic studies - and calendar time. Yet, other confounders could not be taken into account because the information was not available for the total background population.
- Exposure information is based on the Swedish Prescribed Drug Registry, which is initiated in July 2005 and has a complete nationwide coverage.

Introduction

Inflammatory processes in tumour tissue are likely to contribute to tumour progression, immunosuppression and facilitate tumour growth, and cancer susceptibility and severity may also depend on different inflammatory responses.[1] Therefore, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are among the most promising candidates for chemoprevention of cancer, in particular tumours of the gastrointestinal tract. Despite the different indications for maintenance use of aspirin and non-aspirin NSAIDs, the underlying mechanisms are similar.[2 3] NSAIDs inhibit cyclo-oxygenase (COX), an enzyme responsible for the formation of thromboxane (a lipid acting as a vasoconstrictor, which also facilitates platelet aggregation) and prostaglandins (a messenger molecule in the inflammatory pathway); yet only aspirin permanently inhibits platelet formation.[4 5] There are 2 types of NSAIDs, inhibiting both COX-1 and COX-2, or only COX-2. COX-1 is expressed in most tissues regulating many physiological processes.[6] By inhibiting prostaglandin synthesis, NSAIDs compromise gastroduodenal defence mechanisms, including reducing blood flow and mucus and bicarbonate secretion, which may lead to dyspepsia and peptic ulcers, for which proton pump inhibitors (PPIs) are often prescribed as prevention or treatment.[5 6] COX-2 is expressed at sites of inflammation, and is the actual target of NSAIDs.[6] In contrast to non-selective COX-inhibitors (i.e. aspirin and most other NSAIDs), COX-2 selective inhibitors or coxibs are also weakly acidic, and therefore avoid substantial accumulation in (and damage of) the gastric mucosa.[6] Clinical studies have shown similar anti-inflammatory effects, a lower risk of gastrointestinal toxicity, yet a higher risk

of cardiovascular morbidity for COX-2 selective inhibitors compared to nonselective COX-inhibitors.[3 7 8] Some of the older NSAIDs are “relatively selective COX-2 inhibitors”, i.e. nabumetone, meloxicam, etodolac and nimesulide.[3]

However, epidemiological evidence to support a chemopreventive effect is still limited, mainly because large numbers are needed with a long follow-up, in particular for relatively rare cancer types. Meta-analyses have pooled the evidence of the gastrointestinal cancer preventive potential of aspirin and other NSAIDs.[9-14] A large meta-analysis[15] and another detailed scientific assessment[16] concluded that a preventive effect on colorectal cancer was especially pronounced in daily and long-term users (>5 years) in both interventional and observational studies,[15 16] with similar findings in recent studies on gastric cancer.[17 18] Yet, these studies used several different definitions of exposure, ranging from a single prescription of aspirin to daily use for >5 years, with too few studied reporting stratified analyses per dosage (or indication e.g. low dose anti-coagulants versus high dose analgesics) to draw reliable conclusions (although low dose has been recommended by individual studies).[15] The statistical power was too low to identify associations with many other types of (gastro-intestinal) cancer, and more, large original studies are needed to assess the potential preventive effect of other NSAIDs.[15]

The role of PPI use on the association between NSAIDs with gastrointestinal cancer is insufficiently understood yet increasingly investigated, with growing evidence of carcinogenic and other long-term side-effects of PPIs.[19-22]

The objective of this study was to assess the association of aspirin and other NSAIDs on the risk of different gastrointestinal cancer types, while also assessing the potential influence of concomitant PPI use.

Material and Methods

This nationwide Swedish population-based cohort study assessed the risk of gastrointestinal cancer in adult NSAIDs users compared to the risk in the entire Swedish background population of the corresponding sex, age and calendar year (7.1-7.6 million adults). [23] [23] [21][21] Participants were enrolled during the study period from July 1, 2005 (the start of the Swedish Prescribed Drug Registry) to December 31, 2012. The cohort members were followed up until the occurrence of any cancer (excluding non-melanoma skin cancer), death or December 31, 2012 (i.e. the end of data collection for the Swedish Cancer Registry), whichever occurred first. Individuals with a history of any cancer were excluded, as well as individuals with a cancer diagnosis within 12 months after inclusion (to avoid reverse causation). The unique 10-digit personal identity number, assigned to each Swedish resident, was used for identification of all participants and for linkages of their individual data between registries. This study was conducted according to a detailed and a-priori established study protocol.

Data collection

The data for the present study were derived from our Chemoprevention of cancer cohort. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's

human research committee, the Regional Ethical Review Board in Stockholm, without need for informed consent (2014/1291-31/4, approved 27 AUG 2014)(see Supplement 1 and [24-26]). This data collection originates from the nationwide complete Swedish Prescribed Drug Registry, and includes all individuals residing in Sweden who have collected at least one dispensed prescription of any commonly prescribed drug between July 1, 2005 and December 31, 2014 (approximately 85% of all Swedish residents); with follow-up for cancer until December 31, 2012. This cohort has been linked to two other high-quality and complete nationwide Swedish registries, i.e. the Swedish Cancer Registry (>96% completeness of all cancers, originated in 1961),[27] and the Swedish Causes of Death Registry (>99% completeness, originated in 1952), by means of the personal identity number.

Exposures

Therapy with systemic NSAIDs was defined as at least 6 months (≥180 days) cumulative exposure during the study period. This was a cumulative exposure based on the defined daily dosage (DDD) per prescribed package, which takes into account the potency of the drug as well as the prescribed quantity. Three main types of NSAIDs were categorized based on their mechanisms of action (selective or non-selective COX inhibition) and drug class (aspirin or non-aspirin NSAIDs) with corresponding Anatomical Therapeutic Chemical classification codes (ATC): 1) aspirin (B01AC06, N02BA), 2) selective COX-2 inhibitors (coxibs, M01AH), and 3) non-selective non-aspirin NSAIDs (remaining M01A codes). Individuals with ≥180 days of exposure to 2 or 3 of these groups were excluded, so the 3 groups are mutually exclusive. Users of

combination preparations including aspirin, i.e. with corticosteroid (M01BA03), PPIs (B01AC56), statins (C10BX), as well as preparations for local (oral) use (A01AD05) were also excluded.

Additionally, the relatively selective COX-2 inhibitors, a subgroup of the non-selective NSAID users, containing meloxicam (M01AC06) and nabumetone (M01AX01), were also analysed separately. Aspirin users were also divided in 2 groups according to their ATC code (≥180 days): low dose (B01AC06), and high dose aspirin (N02BA) (those using both for ≥180 days were excluded).[28] High-dose aspirin (N02BA) and some other NSAIDs (Diclofenac, M01AB05 and Ibuprofen, M01AE01) are also available over the counter in Sweden, but they are sold in only small packages and at higher prices per dose.[28 29] Thus, we can assume that maintenance users had their doses prescribed, and were thus recorded in the present study.

Outcomes

The outcome was a first gastrointestinal cancer diagnosis recorded in the Swedish Cancer Registry according to the International Classification of Diseases (ICD) 10th edition, including all cancers of the alimentary and hepatobiliary tract. Gastrointestinal cancers were categorized as follows: any gastrointestinal cancer (C15-C26) or cancer of the oesophagus (C15), stomach (C16), small bowel (C17), colorectum (C18-C21), liver, including intrahepatic bile ducts (C22), gallbladder or extrahepatic bile ducts (C23-24), or pancreas (C25). The category “other gastrointestinal cancer” (C26) was not analysed separately. Additionally, the most common histological tumour types were analysed separately: adenocarcinoma (code 096) for oesophageal,

gastric, gallbladder/biliary tract, pancreas and colorectal cancer; squamous cell carcinoma (code 146) for oesophageal cancer; hepatocellular carcinoma (code 066) and cholangiocarcinoma (code 076) for liver cancer; and carcinoid (code 086) for small bowel cancer.

Statistical analyses

The relative risks of developing gastrointestinal cancer in individuals exposed to the drugs under study were standardized using the Swedish background population of the corresponding age, sex, and calendar period. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated, while accounting for changes in age and calendar categories when calculating years of follow-up.[30] Follow-up time was counted from the dispense date of the first NSAID prescription to the date of a first cancer diagnosis, death, or the end of the study (31st December 2012), whichever occurred first. The expected incidence rates were calculated from cancer data recorded in the Swedish Cancer Registry and the age-stratified number of individuals per calendar year according to Statistics Sweden (Population Statistics). The overall SIR for gastrointestinal cancer was calculated, as well as SIRs for each anatomical location separately, including sub-analyses for the most common histological types. The analyses were also stratified for sex and age for each cancer type. Subgroup analyses were performed for high-dose and low-dose aspirin, users of relatively selective COX-2 inhibitors, NSAID use with concurrent PPI (A02BC) or statin (C10AA) use (≥180 days) if the groups were sufficiently large. To assess the effect of PPI and statins, a multivariable Poisson regression model was fitted, adjusting for age at first prescription, sex

and interaction between PPI and statins, and presented as incidence rate ratios (IRR) and 95%CI. The duration of the exposures was assessed by dividing the total cumulative dosage (sum of DDDs per package) received before the cancer diagnosis into four equally sized groups (quartiles), yet their total follow-up time was taken into account for the analyses. There were no missing data on exposures, outcomes or confounding variables. Effect estimates were only reported when at least 5 individuals developed the outcome.

Patient involvement

The Swedish patient organization for cancer of the esophagus, stomach, liver, and pancreas was involved in supporting the present study (www.palema.org). The development of the research question and outcome measures were informed by patients' priorities, experience, and preferences. The results will be disseminated to study participants by means of patient organizations. Patients are thanked in the acknowledgements.

Results

Among all 1,368,027 users of NSAIDs, there were 783,870 (57.3%) aspirin users, 566,209 (41.4%) non-selective NSAIDs users, and 17,948 (1.3%) COX-2 users (Table 1, Supplement 1). Aspirin users were more likely to be male (53.8%) and older than 70 years (54.9.2%), while non-selective NSAID users and COX-2 users were predominantly female (62.8% and 59.9%, respectively) and between 40 and 70 years of age (68.2% and 70.8%, respectively). Use of PPIs was found in 25.6%, 26.2%, and 31.2% of the

aspirin users, non-selective NSAIDs users, and COX-2 users, respectively; and use of statins in 55.2%, 13.7% and 14.4%, respectively. The majority of the population received their first prescription during the first half year of the study period (2005), 54.9% of aspirin users, and 42.5% of non-selective NSAIDs users (Supplement 2).

Aspirin

As presented in Table 1, 10.969 (1.40%) aspirin users developed some type of gastrointestinal cancer during the follow-up. The most common cancer sites were colorectal (n=6,919; 0.88%), gastric (n=1,079; 0.14%), and pancreatic (n=1,114; 0.14%). There was no association with gastrointestinal cancer based on the overall SIRs for aspirin users (SIR=1.02, 95% CI 1.00-1.04) (Table 2). Shorter duration of use (<5.5 years) seemed to be associated with an increased risk for all gastro-intestinal cancers. Yet, longer duration of aspirin use was followed by a decreased SIR for gastrointestinal cancer (SIR=0.31, 95% CI 0.30-0.33 for those with an estimated use between 5.5-7.7 years, and SIR=0.37, 95%CI 0.35-0.40 for >7.7 years) (Table 3) and long-term aspirin users had clearly decreased SIRs for each gastrointestinal cancer type (Table 3). The subgroup analyses including only the low-dosage aspirin users (N=668,305, 85.3% of the aspirin cohort) showed lower SIRs for all cancer locations, with significantly reduced risks for all locations except for oesophageal, gastric and liver cancer (Supplement 3).

Non-selective NSAIDs

Table 1 shows that 3,428 (0.61%) of the non-selective NSAID users developed cancer, mainly colorectal (n=2,017; 0.36%), pancreatic (n=490; 0.09%), and gastric cancers (n=260; 0.05%). Overall, there was a decreased risk of gastrointestinal cancer (SIR=0.79, 95%CI 0.77-0.82), and also for gastric (SIR=0.70, 95% CI 0.62-0.80), colorectal (SIR=0.74, 95% CI 0.71-0.77) and oesophageal (SIR=0.75, 95% CI 0.63-0.89) cancers analysed separately (and their main histological subtypes) (Table 2). There was no evidence of decreased SIRs for the other types of gastrointestinal cancer types, although the effect sizes indicated a decreased SIR of small bowel and liver cancer. Longer duration of use of non-selective NSAIDs was associated with a decreased gastrointestinal cancer risk for all anatomical locations (Table 3).

Selective COX-2 inhibitors

Overall, 100 (0.56%) COX-2 users developed some type of gastrointestinal cancer, predominantly colorectal (n=60; 0.33%), pancreatic (n=13; 0.07%), gastric (n=7; 0.04%), and oesophageal cancers (n=7; 0.04%). There was some evidence for a decreased risk of gastrointestinal cancer overall (SIR=0.89, 95% CI 0.73-1.09), although not statistically significant. None of the sub-analyses showed strong evidence for an association (Supplement 3).

Relatively selective COX-2 inhibitors

Among the non-selective NSAIDs users, 7,609 individuals used relatively selective COX-2 inhibitors, of whom 74 (0.01%) developed cancer. There was

no evidence for an association with any of the gastrointestinal cancer locations (Supplement 3).

Aspirin with PPIs or statins

Users of aspirin with concomitant use of PPIs had higher SIRs for all gastrointestinal cancers compared to those not using PPIs, with all SIRs indicating an increased risk except for gallbladder cancer (Table 4). The SIRs were especially increased for gastric cancer (SIR=1.89; 95% CI 1.73-2.06) and oesophageal cancer (SIR=1.94; 95% CI 1.71-2.20). When using Poisson regression to compare aspirin users using PPIs directly with aspirin users not using PPIs (instead of using the background population as reference), the risk was increased for all gastrointestinal cancers (IRR=1.19, 95% CI 1.11-1.26), with significantly increased risks for oesophageal, gastric, small bowel, liver and pancreatic cancer (Supplement 4).

Among aspirin users exposed to statins, the SIRs were close to unity for each anatomical location (Table 4). When aspirin users using statins were directly compared with aspirin users not using statins, risks were decreased for all gastrointestinal cancers (IRR=0.81, 95% CI 0.77-0.85), with significant decreases for all cancer locations except for colorectal and pancreatic cancer (Supplement 4).

Non-selective NSAIDs with PPIs or statins

In users of non-selective NSAIDs on therapy with PPIs, the SIRs were increased for all gastrointestinal cancer types (and again higher than among

those not using PPIs), except for colorectal cancer (Table 4). When users of non-selective NSAIDs using PPIs were directly compared with those not using PPIs, risks were increased for all gastrointestinal cancers (IRR=1.61, 95% CI 1.49-1.74), and each individual cancer location except for gallbladder cancer (Supplement 4). Among non-selective NSAIDs users using statins, the SIRs were lower than among all users of non-selective NSAIDs, and significantly reduced for oesophageal, gastric and colorectal cancer. When users of non-selective NSAIDs using statins were directly compared with those not using statins, risks were decreased for all gastrointestinal cancers (IRR=0.86, 95% CI 0.76-0.96), yet not significant for the individual cancer locations (Supplement 4).

Discussion

This study on contemporary use of NSAIDs showed a decreased risk of all types of gastrointestinal cancer among long-term users of aspirin (>5.5 years) and non-selective NSAIDs users even for shorter duration of use (>0.7 years). Long-term users of non-selective NSAIDs were at a particularly decreased risk for gastric, oesophageal, and colorectal cancers. These seemingly protective associations might be counteracted by concomitant PPI therapy, and enhanced by concomitant statin use.

The main strengths of this study are the population-based design and large sample size, including all adults residing in Sweden during the study period, which enabled separate analyses for contemporary use of different types of NSAIDs, and evaluation of less common types of gastrointestinal cancer

which could not be assessed previously because of insufficient power, in particular for non-aspirin NSAIDs. Other advantages include the complete follow-up and accurate censoring for mortality. The data on the exposures (medications) and outcomes (gastrointestinal cancers) were highly accurate due to the validity and completeness of the Swedish registries, eliminating recall bias.

Although our findings for aspirin are largely consistent with the literature, that the protective effect is only seen after 5 years, reverse causation, confounding and/or bias appear to influence the aspirin analyses because of the apparent initial increased risk of cancer among short-term users. By excluding all individuals diagnosed with cancer within a year after enrolment, and only including those with a minimal accumulated duration of use of 6 months, the risk of reverse causation should be reduced. Yet, our results indicate that those with an estimated duration shorter than 5 years have an apparent increased risk, which might be because they take aspirin because of yet undiagnosed cancer-related pain or thrombotic events – indicating confounding by indication and reverse causation among the group with the shortest exposure time, an effect which could not have been detected in intervention trials or in case-control studies with a study-design-inherent more restrictive selection of study participants.[15 31] As previous studies reported, 15-20% of cancer patients have thrombotic complications during the course of the disease (often as early manifestation of an occult malignancy),[32] yet these complications (e.g. deep venous thrombosis) are more likely to be treated with anti-coagulants than aspirin. However, when only looking at those

exclusively using low-dose aspirin for ≥180 days, i.e. the platelet aggregation inhibitors, the protective effects were also visible in the overall analyses non taking into account duration, with SIR=0.86 (95%CI 0.85-0.88). This indicates that the apparent increased risks are mainly because of the small group using aspirin as analgesic (high dose), which shows it is important to distinguish between both groups of aspirin-use. Reverse causality seems to be less of a problem for other NSAIDs users, although these may be used as analgesics.[33] Yet, individuals using NSAIDs may be at a lower a-priori risk of developing gastro-intestinal cancer, because individuals with upper gastro-intestinal symptoms are less likely to be chronic NSAIDs users due to the risk of gastro-intestinal side-effects.

Especially for aspirin users (with a high cardiovascular mortality, higher average age than NSAIDs users and more chronic comorbidties), death is a competing risk for the development of cancer, reducing the number at risk to develop cancer. Therefore, we censored follow-up time at time of death. In this cohort the standardised mortality risks were 9.64 (95%CI 9.60-9.69) for aspirin users and 2.08 (95% CI 2.05-2.11) for non-selective non-aspirin NSAIDs users indeed showing a higher risk of death competing with the risk of cancer, leading to an overestimation of the protective effect in particular among aspirin users

Another limitation is potential confounding, e.g. by socio-economic status, dietary factors, obesity, tobacco smoking, and alcohol consumption, which could not be taken into account since such information was not available for the total background population. However, we adjusted for age, sex and

calendar period. Cancer-type specific confounders and their treatment such as *Helicobacter pylori for gastric cancer*, hepatitis B/C infection for liver cancer and chronic inflammatory diseases such as inflammatory bowel disease for bowel cancer and pancreatitis for pancreatic cancer, may also have contributed to the risk of cancer and timing of diagnosis. We may have incomplete exposure ascertainment (and underestimation of duration of use) for part of our cohort since no information was available on prescriptions before July 2005 or over-the-counter use. Yet, potential long-term (protective) effects may be expected to decrease gradually yet significantly after treatment cessation, reducing the potential effect of misclassification on our results due to exposure before 2005. We used the minimal exposure criterion of 180 days to exclude occasional users who are more likely to obtain their NSAIDs over-the-counter, so at a higher price. We did not have data on used daily dosage or duration of use, and used a proxy variable for duration based on accumulation of the average DDDs per package. This explains why some aspirin users had an estimated exposure time longer than the duration of follow-up, indicating a high daily dose. The high variability in actual and estimated administered dosage also hindered assessment of recency of use. Some previous studies subdivided aspirin use into “low dose” and “high dose” based on prescribed dosages (e.g. <75 mg/day[34] or <100 mg/day[14]), but since we did not have information on the number of prescribed pills per day, and different dosages could have been prescribed during the study period, we used the definition based on ATC coding and assessed the estimated duration of use, with the additional advantage that the low-dose aspirin was only available on prescription. This should also be a more accurate reflection

of duration of use than the number of prescriptions.[9] In our study, the DDD per package could range from <5 to 500 (for other NSAIDs) or 1000 (for aspirin), which illustrates the variation between prescriptions. Since 1.4 million individuals were exposed to NSAIDs (≥180 days), i.e. one fifth of the adult population in Sweden, our results are likely to be diluted since we compared them with the total background population. Yet, despite this dilution the associations among long-term users were strongly decreased.

Compared to previous studies, this study was better powered to separately analyses different gastrointestinal cancers and types of NSAIDs.[35] The above mentioned meta-analysis[15] identified only 2 cohort studies including over 100,000 individuals assessing colorectal cancer risk among aspirin-users.[36 37] Even our exposed groups for aspirin and non-selective NSAIDs alone were 5-7 times larger than earlier large studies. The decrease in gastrointestinal cancer risk became evident only after longer exposure, which has also been shown in previous research,[15 38] and is biologically plausible given the expected time latency for (hindering) cancer progression.

The higher risk among aspirin and other NSAID users also using PPIs should be interpreted with some caution. PPIs are often prescribed for gastroesophageal reflux and peptic ulcers, which are risk factors for oesophageal and gastric cancer, respectively. Therefore, a higher cancer risk was expected for those locations, yet not for the other gastrointestinal cancer types. PPIs can also be used to prevent peptic ulcers in users of aspirin and other NSAIDs, usually in individuals without any gastro-intestinal morbidity.

Another study of our group based on the same source cohort,[26] investigated the risk of gastric cancer among PPI maintenance users, which suggested an increased risk in all indication groups for PPI (including those without gastrointestinal symptoms); which also supports a potential independent role for PPI in carcinogenesis as also suggested recently by other groups.[39 40] Together with a potential increased risk of mortality related to long-term PPI use,[41] we believe a more careful approach should be considered when prescribing PPIs to prevent gastrointestinal complications in long-term NSAIDs users. Yet, the risk for gastrointestinal complications such as bleeding should be assessed on an individual bases based on other research investigating shorter-term effects.[42] Before considering implementing aspirin or other NSAIDs as wide-spread intervention, safety, in particular considering long-term use, needs to be considered, with previous research tending towards a “favourable benefit harm-profile” despite an excess risk of bleeding.[43]

To conclude, this large Swedish nationwide and population-based cohort study on contemporary and long-term use of NSAIDs indicates a strongly protective effect of long-term use of both (low-dose) aspirin and other non-selective NSAIDs on gastrointestinal cancer development.

Acknowledgements: We are grateful to all thousands of patients, physicians and healthcare staff members who contributed to the data collection, and to the Swedish National Board of Health and Welfare that collected the data.

Authors' contributions: NB is the submission guarantor. NB and JL had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. NB conducted and is responsible for the data-analysis. Literature search: NB; Design of the study: both authors; Data collection and preparation for analyses: NB; Data analysis: NB; Data interpretation: both authors; Writing of first draft: NB, revised and approved by both authors.

Funding: This work was supported by SFO epidemiology (Karolinska Institutet, junior investigator award NB), Swedish Research Council (839-2008-7496), Swedish Cancer Society (CAN 2015/460). These funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Competing interests: none

Data sharing statement: We are willing to share data upon request after ethics approval has been approved by the relevant committee and the governmental agencies that maintain the data.

References

1. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;**357**(9255):539-45 doi: 10.1016/s0140-6736(00)04046-0[published Online First: Epub Date]|.
2. Simon LS, Yocum D. New and future drug therapies for rheumatoid arthritis. Rheumatology (Oxford) 2000;**39 Suppl 1**:36-42
3. Yang M, Wang HT, Zhao M, et al. Network Meta-Analysis Comparing Relatively Selective COX-2 Inhibitors Versus Coxibs for the Prevention of NSAID-Induced Gastrointestinal Injury. Medicine 2015;**94**(40):e1592 doi: 10.1097/MD.0000000000001592[published Online First: Epub Date]|.
4. Sjodahl R. Nonsteroidal anti-inflammatory drugs and the gastrointestinal tract. Extent, mode, and dose dependence of anticancer effects. Am J Med 2001;**110**(1a):66s-69s
5. Huntjens DR, Danhof M, Della Pasqua OE. Pharmacokinetic-pharmacodynamic correlations and biomarkers in the development of COX-2 inhibitors. Rheumatology (Oxford) 2005;**44**(7):846-59 doi: 10.1093/rheumatology/keh627[published Online First: Epub Date]|.
6. Bjarnason I, Thjodleifsson B. Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs: the effect of nimesulide compared with naproxen on the human gastrointestinal tract. Rheumatology (Oxford) 1999;**38 Suppl 1**:24-32
7. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;**375**(26):2519-29 doi: 10.1056/NEJMoa1611593[published Online First: Epub Date]|.
8. Bakhriansyah M, Souverein PC, de Boer A, et al. Gastrointestinal toxicity among patients taking selective COX-2 inhibitors or conventional NSAIDs, alone or combined with proton pump inhibitors: a case-control study. Pharmacoepidemiol Drug Saf 2017 doi: 10.1002/pds.4183[published Online First: Epub Date]|.

9. Capurso G, Schunemann HJ, Terrenato I, et al. Meta-analysis: the use of non-steroidal anti-inflammatory drugs and pancreatic cancer risk for different exposure categories. Aliment Pharmacol Ther 2007;**26**(8):1089-99 doi: 10.1111/j.1365-2036.2007.03495.x[published Online First: Epub Date]|.
10. Tian W, Zhao Y, Liu S, et al. Meta-analysis on the relationship between nonsteroidal anti-inflammatory drug use and gastric cancer. Eur J Cancer Prev 2010;**19**(4):288-98 doi: 10.1097/CEJ.0b013e328339648c[published Online First: Epub Date]|.
11. Yang P, Zhou Y, Chen B, et al. Aspirin use and the risk of gastric cancer: a meta-analysis. Dig Dis Sci 2010;**55**(6):1533-9 doi: 10.1007/s10620-009-0915-0[published Online First: Epub Date]|.
12. Ye X, Fu J, Yang Y, et al. Dose-risk and duration-risk relationships between aspirin and colorectal cancer: a meta-analysis of published cohort studies. PLoS One 2013;**8**(2):e57578 doi: 10.1371/journal.pone.0057578[published Online First: Epub Date]|.
13. Ye X, Fu J, Yang Y, et al. Frequency-risk and duration-risk relationships between aspirin use and gastric cancer: a systematic review and meta-analysis. PLoS One 2013;**8**(7):e71522 doi: 10.1371/journal.pone.0071522[published Online First: Epub Date]|.
14. Cui XJ, He Q, Zhang JM, et al. High-dose aspirin consumption contributes to decreased risk for pancreatic cancer in a systematic review and meta-analysis. Pancreas 2014;**43**(1):135-40 doi: 10.1097/MPA.0b013e3182a8d41f[published Online First: Epub Date]|.
15. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 2012;**13**(5):518-27 doi: 10.1016/S1470-2045(12)70112-2[published Online First: Epub Date]|.
16. Sutcliffe P, Connock M, Gurung T, et al. Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews. Health Technol Assess 2013;**17**(43):1-253 doi: 10.3310/hta17430[published Online First: Epub Date]|.

17. Cheung KS, Chan EW, Wong AYS, et al. Aspirin and Risk of Gastric Cancer After Helicobacter pylori Eradication: A Territory-Wide Study. LID - 10.1093/jnci/djx267 [doi]. (1460-2105 (Electronic))
18. Niikura R, Hayakawa Y, Hirata Y, et al. Distinct chemopreventive effects of aspirin in diffuse and intestinal-type gastric cancer. LID - canprevres.0276.2017 [pii] LID - 10.1158/1940-6207.CAPR-17-0276 [doi]. (1940-6215 (Electronic))
19. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. Gut 2016;**65**(5):740-8 doi: 10.1136/gutjnl-2015-310376[published Online First: Epub Date]|.
20. Alsalahi O, Dobrian AD. Proton Pump Inhibitors: The Culprit for Barrett's Esophagus? Front Oncol 2014;**4**:373 doi: 10.3389/fonc.2014.00373[published Online First: Epub Date]|.
21. Kia L, Kahrilas PJ. Therapy: Risks associated with chronic PPI use - signal or noise? Nat Rev Gastroenterol Hepatol 2016 doi: 10.1038/nrgastro.2016.44[published Online First: Epub Date]|.
22. Poulsen AH, Christensen S, McLaughlin JK, et al. Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. Br J Cancer 2009;**100**(9):1503-7 doi: 10.1038/sj.bjc.6605024[published Online First: Epub Date]|.
23. Statistics Sweden - Statistical Database Population Statistics (accessed 06 April 2016) http://www.statistikdatabasen.scb.se/. Secondary Statistics Sweden - Statistical Database Population Statistics (accessed 06 April 2016) http://www.statistikdatabasen.scb.se/. http://www.statistikdatabasen.scb.se/.
24. Sadr-Azodi O, Konings P, Brusselaers N. Menopausal hormone therapy and pancreatic cancer risk in women: a population-based matched cohort study. United European gastroenterology journal 2017;**5**(8):1123-28 doi: 10.1177/2050640617702060[published Online First: Epub Date]|.
25. Ma Y, Brusselaers N. Maintenance use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) and prostate cancer risk. Prostate cancer and prostatic diseases 2017 doi: 10.1038/s41391-017-0021-x[published Online First: Epub Date]|.

26. Brusselaers N, Wahlin K, Engstrand L, et al. Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden. BMJ Open 2017;**7**(10):e017739 doi: 10.1136/bmjopen-2017-017739[published Online First: Epub Date]|.
27. Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 2009;**48**(1):27-33 doi: 902131375 [pii]
10.1080/02841860802247664[published Online First: Epub Date]|.
28. FASS (Farmacevtiska specialiteter i Sverige/ Farmaceutical specialities in Sweden), 2015.
29. Läkemedelsverket (Medical Products Agency): Over-the-counter (OTC). Secondary Läkemedelsverket (Medical Products Agency): Over-the-counter (OTC) 2016. https://lakemedelsverket.se/english/product/Medicinal-products/OTC/.
30. Breslow N, Day N. *Statistical Methods in Cancer Research: The design and analysis of cohort studies*. Lyon, 1987.
31. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 2010;**376**(9754):1741-50 doi: 10.1016/S0140-6736(10)61543-7[published Online First: Epub Date]|.
32. Kyriazi V, Theodoulou E. Assessing the risk and prognosis of thrombotic complications in cancer patients. Arch Pathol Lab Med 2013;**137**(9):1286-95 doi: 10.5858/arpa.2012-0490-RA[published Online First: Epub Date]|.
33. Mercadante S. The use of anti-inflammatory drugs in cancer pain. Cancer Treat Rev 2001;**27**(1):51-61 doi: 10.1053/ctrv.2000.0192[published Online First: Epub Date]|.
34. Din FV, Theodoratou E, Farrington SM, et al. Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. Gut 2010;**59**(12):1670-9 doi: 10.1136/gut.2009.203000[published Online First: Epub Date]|.
35. Bosetti C, Rosato V, Gallus S, et al. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol 2012;**23**(6):1403-15 doi: 10.1093/annonc/mds113[published Online First: Epub Date]|.

36. Jacobs EJ, Thun MJ, Bain EB, et al. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst 2007;**99**(8):608-15 doi: 10.1093/jnci/djk132[published Online First: Epub Date]|.
37. Smalley W, Ray WA, Daugherty J, et al. Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. Arch Intern Med 1999;**159**(2):161-6
38. Cao Y, Nishihara R, Wu K, et al. Population-wide Impact of Long-term Use of Aspirin and the Risk for Cancer. JAMA Oncol 2016;**2**(6):762-9 doi: 10.1001/jamaoncol.2015.6396[published Online First: Epub Date]|.
39. Cheung KS, Chan EW, Wong AYS, et al. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut 2018;**67**(1):28-35 doi: 10.1136/gutjnl-2017-314605[published Online First: Epub Date]|.
40. Niikura R, Hayakawa Y, Hirata Y, et al. Long-term proton pump inhibitor use is a risk factor of gastric cancer after treatment for Helicobacter pylori: a retrospective cohort analysis. Gut 2017 doi: 10.1136/gutjnl-2017-315710[published Online First: Epub Date]|.
41. Xie Y, Bowe B, Li T, et al. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. BMJ Open 2017;**7**(6):e015735 doi: 10.1136/bmjopen-2016-015735[published Online First: Epub Date]|.
42. Li L, Geraghty OC, Mehta Z, et al. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017;**390**(10093):490-99 doi: 10.1016/s0140-6736(17)30770-5[published Online First: Epub Date]|.
43. Cuzick J, Thorat MA, Bosetti C, et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol 2015;**26**(1):47-57 doi: 10.1093/annonc/mdu225[published Online First: Epub Date]|.

Table 1: Characteristics of the study cohort on therapy with aspirin, selective cyclo-oxygenase-2 (COX-2) inhibitors, and non-selective non-steroidal anti-inflammatory drug (NSAIDs).

	Aspirin only	Non-selective non-aspirin NSAIDs	Selective COX-2 inhibitors
	Number (%)	*Number (%)*	*Number (%)*
Total	783,870	566,209	17,948
Sex			
Men	421,609 (53.8)	210,705 (37.2)	7,201 (40.1)
Women	362,261 (46.2)	355,504 (62.8)	10,747 (59.9)
Age at first prescription			
<40 years	12,189 (1.6)	110,592 (19.5)	2,720 (15.2)
40-49 years	32,743 (4.2)	125,977 (22.3)	3,849 (21.5)
50-59 years	108,683 (13.9)	146,981 (26.0)	4,941 (27.5)
60-69 years	200,154 (25.5)	112,682 (19.9)	3,914 (21.8)
≥70 years	430,101 (54.9)	69,977 (12.4)	2,524 (14.1)
Calendar period at first prescription			
2005-2006	557,023 (71.1)	387,443 (68.4)	10,393 (57.9)
2007-2009	156,790 (20.0)	145,208 (25.7)	5,500 (30.6)
2010-2012	70,057 (8.9)	33,558 (5.9)	2,055(11.5)
Proton pump inhibitors use (≥180 days)			
yes	200,828 (25.6)	148,586 (26.2)	5,602 (31.2)
no	583,042 (74.4)	417,623 (73.8)	12,346 (68.8)
Statins use (≥180 days)			
yes	432,996 (55.2)	77,514 (13.7)	2,589 (14.4)
no	350,874 (44.8)	488,695 (86.3)	15,359 (85.6)
Gastrointestinal cancer	10,969 (1.40)	3,428 (0.61)	100 (0.56)
Oesophageal cancer	539 (0.07)	134 (0.02)	7 (0.04)
Adenocarcinoma	319 (0.04)	75 (0.01)	4 (0.02)
Squamous cell carcinoma	203 (0.03)	50 (0.01)	2 (0.01)
Gastric cancer	1,079 (0.14)	260 (0.05)	7 (0.04)
Adenocarcinoma	949 (0.12)	212 (0.04)	3 (0.02)
Small bowel cancer	253 (0.03)	94 (0.02)	5 (0.03)
Carcinoid	122 (0.02)	43 (0.01)	2 (0.01)
Colorectal cancer	6,919 (0.88)	2,017 (0.36)	60 (0.33)
Adenocarcinoma	6,608 (0.84)	1,887 (0.33)	59 (0.33)
Liver cancer	645 (0.08)	232 (0.04)	3 (0.02)
Hepatocellular carcinoma	358 (0.05)	100 (0.02)	1 (0.01)
Cholangiocellular carcinoma	81 (0.01)	41 (0.01)	0 (0.00)
Gallbladder and biliary tract cancer	385 (0.05)	190 (0.03)	5 (0.03)
Adenocarcinoma	288 (0.04)	149 (0.03)	2 (0.01)
Pancreatic cancer	1,114 (0.14)	490 (0.09)	13 (0.07)
Adenocarcinoma	835 (0.11)	402 (0.07)	11 (0.06)

Other gastrointestinal cancer	35 (0.00)	11 (0.00)	0 (0.00)
Duration of follow-up in person-years			
Total	3,776,237	3,376,275	82,733
Mean (standard deviation)	4.82 (2.40)	5.96 (1.67)	4.61 (2.21)

Table 2: The risk of different types of gastrointestinal cancer (and the major histological subtype) among users of aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), expressed as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) and stratified by age and sex.

	Aspirin users (n=783,870)		Non-selective non-aspirin NSAIDs users (n=566,209)	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
Gastrointestinal cancer	**10,969**	**1.02 (1.00-1.04)**	**3,428**	**0.79 (0.77-0.82)**
Men	6,659	1.24 (1.21-1.27)	1,390	0.78 (0.74-0.82)
Women	4,310	0.99 (0.96-1.02)	2,038	0.81 (0.77-0.84)
18-39 years	3	-	14	0.59 (0.32-0.99)
40-49 years	20	0.70 (0.43-1.08)	116	0.67 (0.55-0.81)
50-59 years	408	1.13 (1.03-1.25)	423	0.61 (0.55-0.67)
60-69 years	2,286	1.13 (1.08-1.18)	1,074	0.71 (0.67-0.75)
≥70 years	8,252	0.99 (0.97-1.01)	1,801	0.94 (0.90-0.98)
Oesophageal cancer	**539**	**1.10 (1.01-1.19)**	**134**	**0.75 (0.63-0.89)**
Adenocarcinoma	319	1.17 (1.04-1.30)	75	0.81 (0.64-1.01)
Squamous cell carcinoma	203	1.06 (0.92-1.22)	50	0.66 (0.49-0.87)
Men	415	1.09 (0.99-1.20)	90	0.88 (0.63-0.97)
Women	124	1.12 (0.93-1.33)	44	0.68 (0.49-0.91)
18-39 years	0	-	0	-
40-49 years	1	-	5	0.87 (0.28-2.03)
50-59 years	21	0.99 (0.61-1.51)	18	0.58 (0.34-0.92)
60-69 years	164	1.35 (1.15-1.57)	47	0.65 (0.48-0.86)
≥70 years	353	1.02 (0.92-1.13)	64	0.92 (0.71-1.18)
Gastric cancer	**1,079**	**1.08 (1.01-1.14)**	**260**	**0.70 (0.62-0.80)**
Adenocarcinoma	949	1.07 (1.00-1.14)	212	0.66 (0.58-0.76)
Men	714	1.08 (1.00-1.16)	128	0.72 (0.60-0.85)
Women	365	1.08 (0.97-1.19)	132	0.69 (0.58-0.82)
18-39 years	0	-	1	-
40-49 years	3	-	13	0.71 (0.38-1.22)
50-59 years	51	1.48 (1.10-1.94)	37	0.61 (0.43-0.85)
60-69 years	208	1.20 (1.04-1.37)	73	0.61 (0.48-0.77)
≥70 years	817	1.03 (0.96-1.11)	136	0.81 (0.68-0.95)
Small bowel cancer	**253**	**1.05 (0.93-1.19)**	**94**	**0.84 (0.68-1.02)**
Carcinoid	122	1.11 (0.92-1.32)	43	0.84 (0.61-1.13)
Men	150	1.05 (0.89-1.23)	34	0.72 (0.50-1.00)
Women	103	1.06 (0.86-1.28)	60	0.93 (0.71-1.19)
18-39 years	0	-	1	-
40-49 years	1	-	3	-
50-59 years	18	1.53 (0.91-2.41)	18	0.77 (0.46-1.22)

60-69 years	64	1.16 (0.89-1.48)	33	0.81 (0.56-1.14)
≥70 years	170	0.99 (0.85-1.15)	39	0.98 (0.69-1.34)
Colorectal cancer	**6,919**	**1.00 (0.98-1.03)**	**2,017**	**0.74 (0.71-0.77)**
Adenocarcinoma	6,608	1.00 (0.80-1.03)	1,887	0.74 (0.70-0.77)
Men	4,105	1.03 (1.00-1.06)	793	0.73 (0.68-0.79)
Women	2,814	0.97 (0.93-1.00)	1,224	0.74 (0.70-0.78)
18-39 years	2	-	10	0.61 (0.29-1.13)
40-49 years	9	0.52 (0.24-0.98)	51	0.47 (0.35-0.62)
50-59 years	241	1.16 (1.02-1.31)	232	0.55 (0.48-0.63)
60-69 years	1,268	1.05 (0.99-1.11)	600	0.66 (0.60-0.71)
≥70 years	5,399	0.99 (0.96-1.02)	1,124	0.88 (0.83-0.94)
Liver cancer	**645**	**1.11 (1.03-1.20)**	**232**	**0.96 (0.84-1.09)**
Hepatocellular carcinoma	358	1.13 (1.02-1.25)	100	0.83 (0.77-1.01)
Cholangiocellular carcinoma	81	1.14 (0.91-1.42)	41	1.10 (0.79-1.49)
Men	449	1.12 (1.02-1.23)	130	1.00 (0.84-1.19)
Women	196	1.09 (0.94-1.26)	102	0.91 (0.74-1.10)
18-39 years	0	-	3	-
40-49 years	4	-	10	0.95 (0.46-1.75)
50-59 years	32	1.04 (0.71-1.47)	44	0.90 (0.65-1.21)
60-69 years	182	1.36 (1.17-1.57)	90	0.99 (0.79-1.21)
≥70 years	427	1.03 (0.94-1.14)	85	0.95 (0.76-1.17)
Gallbladder and biliary tract cancer	**385**	**0.92 (0.83-1.01)**	**190**	**1.03 (0.89-1.19)**
Adenocarcinoma	288	0.93 (0.82-1.04)	149	1.07 (0.90-1.25)
Men	181	1.00 (0.86-1.15)	50	0.98 (0.73-1.29)
Women	204	0.85 (0.74-0.80)	140	1.05 (0.88-1.24)
18-39 years	0	-	1	-
40-49 years	0	-	7	0.97 (0.39-2.00)
50-59 years	6	0.52 (.19-1.13)	12	0.46 (0.24-0.80)
60-69 years	91	1.31 (1.05-1.60)	63	1.00 (0.77-1.28)
≥70 years	288	0.85 (0.76-0.96)	107	1.23 (1.00-1.48)
Pancreatic cancer	**1,114**	**1.04 (0.98-1.11)**	**490**	**1.00 (0.92-1.10)**
Adenocarcinoma	835	1.00 (0.93-1.07)	402	1.02 (0.92-1.13)
Men	629	1.07 (0.99-1.16)	163	0.89 (0.76-1.03)
Women	485	1.01 (0.92-1.11)	327	1.08 (0.96-1.20)
18-39 years	1	-	1	-
40-49 years	3	-	26	1.65 (1.08-2.42)
50-59 years	37	0.91 (0.64-1.25)	68	0.86 (0.67-1.09)
60-69 years	307	1.19 (1.06-1.33)	174	0.85 (0.73-0.99)
≥70 years	766	1.00 (0.93-1.07)	221	1.18 (1.03-1.35)

Table 3: The risk of gastrointestinal cancer among aspirin and non-aspirin non-steroidal anti-inflammatory drug (NSAID) users, by estimated duration of use, expressed as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs).

	Aspirin only (n=783,870)			Non-selective non-aspirin NSAIDs (n=566,209)		
	Categories (quartiles)	*Number of cases*	*SIRs (95% CI)*	*Categories (quartiles)*	*Number of cases*	*SIRs (95% CI)*
Gastrointestinal cancer						
	0.5-2.5 years	4,158	2.77 (2.69-2.85)	*0.5-0.7 years*	865	1.00 (0.93-1.06)
	2.5-5.5 years	4,532	1.83 (1.77-1.88)	*0.7-1.1 years*	832	0.92 (0.86-0.98)
	5.5-7.7 years	1,310	0.31 (0.30-0.33)	*1.1-2.1 years*	977	0.86 (0.80-0.91)
	>7.7 years	969	0.37 (0.35-0.40)	*>2.1 years*	754	0.54 (0.50-0.58)
Oesophageal cancer						
	0.5-2.5 years	204	2.91 (2.52-3.33)	*0.5-0.7 years*	35	0.93 (0.65-1.29)
	2.5-5.5 years	216	1.83 (1.60-2.09)	*0.7-1.1 years*	32	0.84 (0.57-1.18)
	5.5-7.7 years	61	0.31 (0.24-0.40)	*1.1-2.1 years*	43	0.91 (0.66-1.23)
	>7.7 years	58	0.56 (0.42-0.72)	*>2.1 years*	23	0.41 (0.26-0.61)
Gastric cancer						
	0.5-2.5 years	61	2.89 (2.62-3.19)	*0.5-0.7 years*	55	0.73 (0.55-0.95)
	2.5-5.5 years	466	2.00 (1.82-2.19)	*0.7-1.1 years*	61	0.78 (0.60-1.01)
	5.5-7.7 years	99	0.26 (0.21-0.31)	*1.1-2.1 years*	80	0.82 (0.65-1.02)
	>7.7 years	110	0.45 (0.37-0.55)	*>2.1 years*	64	0.54 (0.42-0.69)
Small bowel cancer						
	0.5-2.5 years	96	2.78 (2.25-3.39)	*0.5-0.7 years*	22	0.94 (0.59-1.43)
	2.5-5.5 years	109	1.94 (1.59-2.33)	*0.7-1.1 years*	20	0.83 (0.51-1.29)
	5.5-7.7 years	26	0.28 (0.18-0.41)	*1.1-2.1 years*	25	0.85 (0.55-1.25)
	>7.7 years	22	0.39 (0.25-0.60)	*>2.1 years*	27	0.76 (0.50-1.11)
Colorectal cancer						
	0.5-2.5 years	2,658	2.78 (2.67-2.88)	*0.5-0.7 years*	540	0.99 (0.91-1.08)
	2.5-5.5 years	2,844	1.79 (1.73-1.86)	*0.7-1.1 years*	489	0.86 (0.78-0.94)

	5.5-7.7 years	813	0.31 (0.29-0.33)	*1.1-2.1 years*	565	0.78 (0.72-0.85)
	>7.7 years	604	0.36 (0.33-0.39)	*>2.1 years*	423	0.47 (0.43-0.52)
Liver cancer						
	0.5-2.5 years	222	2.63 (2.30-3.00)	*0.5-0.7 years*	63	1.23 (0.95-1.57)
	2.5-5.5 years	272	1.96 (1.74-2.21)	*0.7-1.1 years*	53	1.02 (0.76-1.33)
	5.5-7.7 years	100	0.44 (0.35-0.53)	*1.1-2.1 years*	70	1.10 (0.86-1.39)
	>7.7 years	51	0.40 (0.30-0.53)	*>2.1 years*	46	0.61 (0.45-0.81)
Gallbladder and biliary tract cancer						
	0.5-2.5 years	137	2.36 (1.98-2.79)	*0.5-0.7 years*	42	1.17 (0.85-1.58)
	2.5-5.5 years	143	1.52 (1.28-1.79)	*0.7-1.1 years*	51	1.34 (1.00-1.76)
	5.5-7.7 years	61	0.39 (0.30-.50)	*1.1-2.1 years*	52	1.06 (0.79-1.39)
	>7.7 years	44	0.40 (0.29-0.53)	*>2.1 years*	45	0.73 (0.53-0.98)
Pancreatic cancer						
	0.5-2.5 years	424	2.79 (2.53-3.06)	*0.5-0.7 years*	107	1.09 (0.90-1.32)
	2.5-5.5 years	467	1.87 (1.71-2.06)	*0.7-1.1 years*	123	1.20 (1.00-1.43)
	5.5-7.7 years	149	0.36 (0.30-0.42)	*1.1-2.1 years*	136	1.05 (0.88-1.25)
	>7.7 years	74	0.28 (0.23-0.37)	*>2.1 years*	124	0.78 (0.65-0.93)

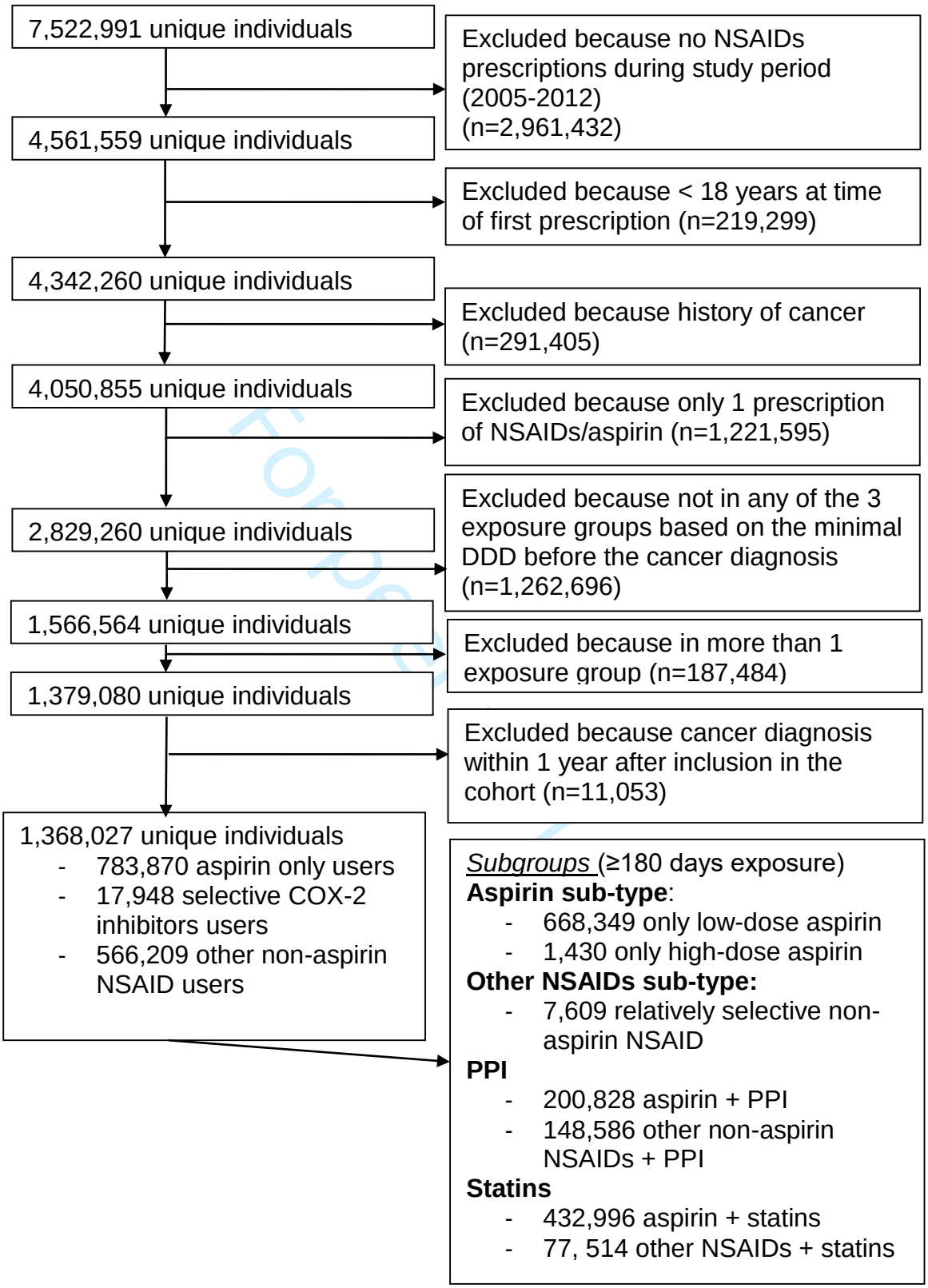
Table 4: The risk of gastrointestinal cancer among aspirin and non-selective non-aspirin non-steroidal anti-inflammatory drug (NSAID) users, stratified by additional use of proton pump inhibitors (PPIs) or statins compared to the total Swedish background population, expressed as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs).

	Aspirin users (n=783,870)		Aspirin with PPI (n=200,828)		Aspirin with statins (n=432,996)	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
All gastrointestinal cancer	10,969	1.02 (1.00-1.04)	3,617	1.25 (1.21-2.29)	6,210	0.99 (0.96-1.01)
Oesophageal cancer	539	1.10 (1.01-1.19)	247	1.94 (1.71-2.20)	299	0.98 (0.87-1.09)
Gastric cancer	1,079	1.08 (1.01-1.14)	509	1.89 (1.73-2.06)	619	1.05 (0.98-1.13)
Small bowel cancer	253	1.05 (0.93-1.19)	107	1.67 (1.37-2.01)	139	0.97 (0.81-1.14)
Colorectal cancer	6,919	1.00 (0.98-1.03)	2,004	1.07 (1.02-1.12)	3,893	0.97 (0.94-1.00)
Liver cancer	645	1.11 (1.03-1.20)	231	1.52 (1.33-1.73)	351	0.99 (0.89-1.10)
Gallbladder and biliary tract cancer	385	0.92 (0.83-1.01)	117	1.00 (0.82-1.19)	212	0.90 (0.78-1.03)
Pancreatic cancer	1,114	1.04 (0.98-1.11)	391	1.36 (1.23-1.50)	678	1.07 (0.99-2.15)

	Non-aspirin NSAIDs users (n=567,569)		Non-selective non-aspirin with PPI (n=148,586)		Non-selective non-aspirin with statins (n=77,514)	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
All gastrointestinal cancer	3,428	0.79 (0.77-0.82)	1,360	1.08 (1.02-1.13)	625	0.71 (0.65-0.76)
Oesophageal cancer	134	0.75 (0.63-0.89)	67	1.36 (1.05-1.73)	24	0.64 (0.41-0.95)
Gastric cancer	260	0.70 (0.62-0.80)	156	1.47 (1.25-1.72)	44	0.58 (0.42-0.78)
Small bowel cancer	94	0.84 (0.68-1.02)	45	1.39 (1.02-1.87)	14	0.64 (0.35-1.07)
Colorectal cancer	2,017	0.74 (0.71-0.77)	694	0.86 (0.80-0.93)	380	0.68 (0.61-0.75)
Liver cancer	232	0.96 (0.84-1.09)	102	1.51 (1.23-1.83)	38	0.78 (0.55-1.07)
Gallbladder and biliary tract cancer	190	1.03 (0.89-1.19)	68	1.21 (0.94-1.53)	29	0.76 (0.51-1.10)
Pancreatic cancer	490	1.00 (0.92-1.10)	222	1.55 (1.35-1.76)	93	0.92 (0.75-1.13)

Online Supplement 1

Description of original cohort, the “Chemoprevention of Cancer” cohort, and flow-chart describing the selection of the study cohort.



Abbreviations: COX, cyclooxygenase; DDD, defined daily dosage; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors

This cohort included all individuals residing in Sweden who received at least one dispensed prescription of one of the following commonly prescribed drugs between July 1, 2005 and December 31, 2014 (with corresponding ATC codes) with follow-up for cancer until December 2012: sex hormones (G03), drugs for peptic ulcers and gastro-esophageal reflux disease (A02B), acetylsalicylic acid (B01AC06, N02BA), non-steroidal anti-inflammatory drugs (M01A), HMG CoA reductase inhibitors (C10AA), drugs affecting bone structure and mineralization, (M05B), and antibiotics (J01AA, J01CA04, J01FA, J01MA, J01XD, J01XE, J04AB04). This cohort included approximately 85% of all Swedish residents, with especially high coverage of adults.

Supplement 2: Year of first prescription among aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) users during the study period.

	Aspirin	Non-aspirin NSAIDs
	N (%)	*N (%)*
2005	430,391 (54.9)	240,848 (42.5)
2006	79,356 (10.1)	143,805 (25.4)
2007	60,071 (7.7)	71,053 (12.6)
2008	55,527 (7.1)	46,013 (8.1)
2009	49,885 (6.4)	29,814 (5.3)
2010	43,290 (5.5)	18,957 (3.4)
2011	38,415 (4.9)	11,736 (2.1)
2012	26,935 (3.4)	3,983 (0.7)
Total	783,87	566,209

Supplement 3: The risk of gastrointestinal cancer among maintenance users of cyclo-oxygenase-2 (COX-2) selective inhibitors and relatively selective COX-2 inhibitors, and low-dose aspirin users, presented as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs).

	COX-2 selective inhibitors maintenance users (n=17,948)		**Relatively selective COX-2 inhibitors maintenance users (n=7,609)**		**Low-dose aspirin (n=668,305)**	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
Gastrointestinal cancer	100	0.89 (0.73-1.09)	74	0.97 (0.76-1.21)	9,996	0.86 (0.85-0.88)
Oesophageal cancer	7	1.49 (0.60-3.07)	1	-	493	0.99 (0.91-1.08)
Gastric cancer	7	0.74 (0.30-1.52)	4	-	986	0.94 (0.88-1.00)
Small bowel cancer	5	1.72 (0.55-4.00)	3	-	224	0.84 (0.74-0.96)
Colorectal cancer	60	0.85 (0.65-1.09)	50	1.02 (0.76-1.35)	6,338	0.85 (0.83-0.88)
Liver cancer	3	-	3	-	592	0.97 (0.89-1.05)
Gallbladder and biliary tract cancer	5	1.05 (0.34-2.44)	3	-	344	0.74 (0.66-0.82)
Pancreatic cancer	13	1.02 (0.54-1.74)	10	1.15 (0.55-2.12)	990	0.80 (0.75-0.85)

Supplement 4: The risk of gastrointestinal cancer among aspirin and non-selective non-aspirin non-steroidal anti-inflammatory drug (NSAID) users comparing users with non-users of additional proton pump inhibitors (PPI) or statins, calculated with Poisson Regression models and expressed as incidence rate ratios (IRR) and 95% confidence intervals (CIs).

	Aspirin with PPI vs. without	Aspirin with statin vs. without	Non-selective non-aspirin NSAIDs with PPI vs. without	Non-selective non-aspirin NSAIDs with statins vs. without
	IRR (95% CI)	*IRR (95% CI)*	*IRR (95% CI)*	*IRR (95% CI)*
All gastrointestinal cancer	1.19 (1.11-1.26)	0.81 (0.77-0.85)	1.61 (1.49-1.74)	0.86 (0.76-0.96)
Oesophageal cancer	2.16 (1.67-2.80)	0.59 (0.47-0.75)	2.58 (1.77-3.75)	0.65 (0.32-1.31)
Gastric cancer	2.26 (1.88-2.71)	0.81 (0.69-0.96)	3.68 (2.80-4.83)	0.62 (0.34-1.11)
Small bowel cancer	1.65 (1.12-2.42)	0.65 (0.47-0.90)	2.20 (1.41-3.42)	0.62 (0.26-1.47)
Colorectal cancer	0.98 (0.90-1.06)	0.85 (0.80-1.90)	1.30 (1.17-1.44)	0.94 (0.81-1.08)
Liver cancer	1.56 (1.23-1.99)	0.64 (0.53-0.78)	2.12 (1.59-2.82)	0.79 (0.49-1.27)
Gallbladder and biliary tract cancer	0.70 (0.49-1.02)	0.67 (0.52-0.86)	1.28 (0.92-1.77)	0.67 (0.40-1.11)
Pancreatic cancer	1.32 (1.08-1.62)	0.90 (0.77-1.04)	1.88 (1.54-2.30)	0.78 (0.55-1.09)

Adjusted for age at first prescription, sex, and interaction between PPI and statins

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

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p 1 & 3 (abstract & title)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p 5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	p 6
Methods			
Study design	4	Present key elements of study design early in the paper	p 7-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p 7-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	p 7-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p 7-10 + appendix
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	p 7-10
Bias	9	Describe any efforts to address potential sources of bias	p 7-10
Study size	10	Explain how the study size was arrived at	Fig 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p 7-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p 9-10
		(*b*) Describe any methods used to examine subgroups and interactions	p 9-10
		(*c*) Explain how missing data were addressed	p 9-10
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
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	Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p 11, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 1-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	Tables 2-4

		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	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p 11-13, appendix
Discussion			
Key results	18	Summarise key results with reference to study objectives	p 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	p 14-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p 14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	p 14-17
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	p 3, p 17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Maintenance use of non-steroidal anti-inflammatory drugs and risk of gastrointestinal cancer in a nationwide population-based cohort study in Sweden

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-021869.R2
Article Type:	Research
Date Submitted by the Author:	17-May-2018
Complete List of Authors:	Brusselaers, Nele; Karolinska Institutet, Molecular medicine and Surgery Lagergren, Jesper; Karolinska Institutet, Department of Molecular medicine and Surgery; King's College London, Division of Cancer Studies
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Oncology, Pharmacology and therapeutics
Keywords:	Gastrointestinal tumours < GASTROENTEROLOGY, chemoprevention, non-steroidal antiinflammatory drugs, aspirin, coxibs, cancer

Maintenance use of non-steroidal anti-inflammatory drugs and risk of gastrointestinal cancer in a nationwide population-based cohort study in Sweden.

Running title: NSAIDs and gastrointestinal cancer prevention

Authors: Nele BRUSSELAERS[1,2], MD MSc PhD, Jesper LAGERGREN[3,4], MD PhD.

Affiliations:

[1] Centre for Translational Microbiome Research, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Karolinska Hospital, Stockholm, Sweden

[2] Science for Life Laboratory (SciLifeLab), Stockholm, Sweden

[3] Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

[4] Division of Cancer Studies, King's College London, United Kingdom.

Correspondence and requests for reprints: Dr. Nele Brusselaers, Centre for Translational Microbiome Research, Department of Microbiology, Tumor and Cell biology, Karolinska Institutet, Nobelsvag16, 171 77 Stockholm, Sweden.
E-mail: Nele.Brusselaers@ki.se, Tel: +46 8 524 853 08
***Email addresses authors*:** nele.brusselaers@ki.se; jesper.lagergren@ki.se

Word count*: 3,7772 words; Tables: 4, Figures: 0; supplement: 4*

Structured summary (239 words)

Objectives: Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are potential candidates for chemoprevention of gastrointestinal cancer. We aimed to assess the association between contemporary NSAID use (≥180 days) and gastrointestinal cancer.

Design: Nationwide Swedish population-based cohort study (2005-2012,

Setting: Sweden

Participants: All adults exposed to maintenance NSAIDs use (aspirin, n=783,870; unselective NSAIDs, n=566,209, selective COX-2 inhibitors, n=17,948) compared to the Swedish background population of the same age, sex and calendar period.

Outcome measures: the risk of different gastro-intestinal cancer types expressed as standardized incidence ratios (SIR) and 95% confidence intervals (CI), taking into account concurrent proton-pump-inhibitors (PPIs) and statins usage.

Results: The SIR for gastro-intestinal cancer for aspirin-use was 1.02 (95%CI 1.00-1.04), with clearly reduced risk for long-term users (SIR=0.31, 95%CI 0.30-0.33 for 5.5-7.7 years), but an increased risk for short-term users (SIR=2.77, 95% CI 2.69-2.85), and stronger protective effect for low-dose aspirin (SIR=0.86, 95% CI 0.85-0.88). Users of non-selective NSAIDs showed an overall decreased risk of gastrointestinal cancer (SIR=0.79, 95%CI 0.77-0.82), in particular for cancer of the stomach, colorectum and oesophagus, and the SIRs were further decreased among long-term users. Users of selective COX-2 inhibitors showed a SIR=0.89 (95%CI 0.73-1.09) for gastrointestinal cancers. Both aspirin and unselective NSAIDs users who also

were using PPIs, had higher risks for all gastrointestinal cancer types; and lower risk if using statins.

Conclusion: Long-term use of (low-dose) aspirin and non-selective NSAIDs was associated with a decreased risk of all gastrointestinal cancer types.

Key words: gastro-intestinal cancer, chemoprevention, non-steroidal anti-inflammatory drugs, aspirin, coxibs, cancer, pharmaco-epidemiology.

Article summary: Strengths and limitations of this study

- Population-based and nationwide design based on contemporary use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) – resulting in sufficient power to assess less common types of gastrointestinal cancer, and different formulations of NSAIDs.
- Concurrent maintenance use of statins and proton pump inhibitors is assessed.
- This study is based on real-life user information because of the population-based design, which leads to inherent problems of confounding by indication and reverse causality which were taken into account in the design and analyses.
- The findings are standardized for age, sex – which are often described as the major confounding factors in epidemiologic studies - and calendar time. Yet, other confounders could not be taken into account because the information was not available for the total background population.
- Exposure information is based on the Swedish Prescribed Drug Registry, which is initiated in July 2005 and has a complete nationwide coverage.

Introduction

Inflammatory processes in tumour tissue are likely to contribute to tumour progression, immunosuppression and facilitate tumour growth, and cancer susceptibility and severity may also depend on different inflammatory responses.[1] Therefore, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are among the most promising candidates for chemoprevention of cancer, in particular tumours of the gastrointestinal tract. Despite the different indications for maintenance use of aspirin and non-aspirin NSAIDs, the underlying mechanisms are similar.[2 3] NSAIDs inhibit cyclo-oxygenase (COX), an enzyme responsible for the formation of thromboxane (a lipid acting as a vasoconstrictor, which also facilitates platelet aggregation) and prostaglandins (a messenger molecule in the inflammatory pathway); yet only aspirin permanently inhibits platelet formation.[4 5] There are 2 types of NSAIDs, inhibiting both COX-1 and COX-2, or only COX-2. COX-1 is expressed in most tissues regulating many physiological processes.[6] By inhibiting prostaglandin synthesis, NSAIDs compromise gastroduodenal defence mechanisms, including reducing blood flow and mucus and bicarbonate secretion, which may lead to dyspepsia and peptic ulcers, for which proton pump inhibitors (PPIs) are often prescribed as prevention or treatment.[5 6] COX-2 is expressed at sites of inflammation, and is the actual target of NSAIDs.[6] In contrast to non-selective COX-inhibitors (i.e. aspirin and most other NSAIDs), COX-2 selective inhibitors or coxibs are also weakly acidic, and therefore avoid substantial accumulation in (and damage of) the gastric mucosa.[6] Clinical studies have shown similar anti-inflammatory effects, a lower risk of gastrointestinal toxicity, yet a higher risk

of cardiovascular morbidity for COX-2 selective inhibitors compared to nonselective COX-inhibitors.[3 7 8] Some of the older NSAIDs are “relatively selective COX-2 inhibitors”, i.e. nabumetone, meloxicam, etodolac and nimesulide.[3]

However, epidemiological evidence to support a chemopreventive effect is still limited, mainly because large numbers are needed with a long follow-up, in particular for relatively rare cancer types. Meta-analyses have pooled the evidence of the gastrointestinal cancer preventive potential of aspirin and other NSAIDs.[9-14] A large meta-analysis[15] and another detailed scientific assessment[16] concluded that a preventive effect on colorectal cancer was especially pronounced in daily and long-term users (>5 years) in both interventional and observational studies,[15 16] with similar findings in recent studies on gastric cancer.[17 18] Yet, these studies used several different definitions of exposure, ranging from a single prescription of aspirin to daily use for >5 years, with too few studied reporting stratified analyses per dosage (or indication e.g. low dose anti-coagulants versus high dose analgesics) to draw reliable conclusions (although low dose has been recommended by individual studies).[15] The statistical power was too low to identify associations with many other types of (gastro-intestinal) cancer, and more, large original studies are needed to assess the potential preventive effect of other NSAIDs.[15]

The role of PPI use on the association between NSAIDs with gastrointestinal cancer is insufficiently understood yet increasingly investigated, with growing evidence of carcinogenic and other long-term side-effects of PPIs[19-22] as also shown by our group.[23-25]

The objective of this study was to assess the association of aspirin and other NSAIDs on the risk of different gastrointestinal cancer types, while also assessing the potential influence of concomitant PPI use.

Material and Methods

This nationwide Swedish population-based cohort study assessed the risk of gastrointestinal cancer in adult NSAIDs users,[26] compared to the risk in the entire Swedish background population of the corresponding sex, age and calendar year (7.1-7.6 million adults) as provided by Statistics Sweden. [27] [27] [27] Participants were enrolled during the study period from July 1, 2005 (the start of the Swedish Prescribed Drug Registry) to December 31, 2012, as described in more detail elsewhere.[23 25 28 29] The cohort members were followed up until the occurrence of any cancer (excluding non-melanoma skin cancer), death or December 31, 2012 (i.e. the end of data collection for the Swedish Cancer Registry), whichever occurred first. Individuals with a history of any cancer were excluded, as well as individuals with a cancer diagnosis within 12 months after inclusion (to avoid reverse causation). The unique 10-digit personal identity number, assigned to each Swedish resident, was used for identification of all participants and for linkages of their individual data between registries. This study was conducted according to a detailed and a-priori established study protocol.

Data collection

The data for the present study were derived from our Chemoprevention of cancer cohort. The study protocol conforms to the ethical guidelines of the

1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee, the Regional Ethical Review Board in Stockholm, without need for informed consent (2014/1291-31/4, approved 27 AUG 2014)(see Supplement 1 and [25 26 30]). This data collection originates from the nationwide complete Swedish Prescribed Drug Registry, and includes all individuals residing in Sweden who have collected at least one dispensed prescription of any commonly prescribed drug between July 1, 2005 and December 31, 2014 (approximately 85% of all Swedish residents); with follow-up for cancer until December 31, 2012. This cohort has been linked to two other high-quality and complete nationwide Swedish registries, i.e. the Swedish Cancer Registry (>96% completeness of all cancers, originated in 1961),[31] and the Swedish Causes of Death Registry (>99% completeness, originated in 1952), by means of the personal identity number.

Exposures

Therapy with systemic NSAIDs was defined as at least 6 months (≥180 days) cumulative exposure during the study period. This was a cumulative exposure based on the defined daily dosage (DDD) per prescribed package, which takes into account the potency of the drug as well as the prescribed quantity. Three main types of NSAIDs were categorized based on their mechanisms of action (selective or non-selective COX inhibition) and drug class (aspirin or non-aspirin NSAIDs) with corresponding Anatomical Therapeutic Chemical classification codes (ATC): 1) aspirin (B01AC06, N02BA), 2) selective COX-2 inhibitors (coxibs, M01AH), and 3) non-selective non-aspirin NSAIDs (remaining M01A codes). Individuals with ≥180 days of exposure to 2 or 3 of

these groups were excluded, so the 3 groups are mutually exclusive. Users of combination preparations including aspirin, i.e. with corticosteroid (M01BA03), PPIs (B01AC56), statins (C10BX), as well as preparations for local (oral) use (A01AD05) were also excluded.

Additionally, the relatively selective COX-2 inhibitors, a subgroup of the non-selective NSAID users, containing meloxicam (M01AC06) and nabumetone (M01AX01), were also analysed separately. Aspirin users were also divided in 2 groups according to their ATC code (≥180 days): low dose (B01AC06), and high dose aspirin (N02BA) (those using both for ≥180 days were excluded).[32] High-dose aspirin (N02BA) and some other NSAIDs (Diclofenac, M01AB05 and Ibuprofen, M01AE01) are also available over the counter in Sweden, but they are sold in only small packages and at higher prices per dose.[32 33] Thus, we can assume that maintenance users had their doses prescribed, and were thus recorded in the present study.

Outcomes

The outcome was a first gastrointestinal cancer diagnosis recorded in the Swedish Cancer Registry according to the International Classification of Diseases (ICD) 10th edition, including all cancers of the alimentary and hepatobiliary tract. Gastrointestinal cancers were categorized as follows: any gastrointestinal cancer (C15-C26) or cancer of the oesophagus (C15), stomach (C16), small bowel (C17), colorectum (C18-C21), liver, including intrahepatic bile ducts (C22), gallbladder or extrahepatic bile ducts (C23-24), or pancreas (C25). The category “other gastrointestinal cancer” (C26) was not analysed separately. Additionally, the most common histological tumour types

were analysed separately: adenocarcinoma (code 096) for oesophageal, gastric, gallbladder/biliary tract, pancreas and colorectal cancer; squamous cell carcinoma (code 146) for oesophageal cancer; hepatocellular carcinoma (code 066) and cholangiocarcinoma (code 076) for liver cancer; and carcinoid (code 086) for small bowel cancer.

Statistical analyses

The relative risks of developing gastrointestinal cancer in individuals exposed to the drugs under study were standardized using the Swedish background population of the corresponding age, sex, and calendar period. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated, while accounting for changes in age and calendar categories when calculating years of follow-up.[34] Follow-up time was counted from the dispense date of the first NSAID prescription to the date of a first cancer diagnosis, death, or the end of the study (31st December 2012), whichever occurred first. The expected incidence rates were calculated from cancer data recorded in the Swedish Cancer Registry and the age-stratified number of individuals per calendar year according to Statistics Sweden (Population Statistics). The overall SIR for gastrointestinal cancer was calculated, as well as SIRs for each anatomical location separately, including sub-analyses for the most common histological types. The analyses were also stratified for sex and age for each cancer type. Subgroup analyses were performed for high-dose and low-dose aspirin, users of relatively selective COX-2 inhibitors, NSAID use with concurrent PPI (A02BC) or statin (C10AA) use (≥180 days) if the groups were sufficiently large. To assess the effect of PPI and statins, a multivariable

Poisson regression model was fitted, adjusting for age at first prescription, sex and interaction between PPI and statins, and presented as incidence rate ratios (IRR) and 95%CI. The duration of the exposures was assessed by dividing the total cumulative dosage (sum of DDDs per package) received before the cancer diagnosis into four equally sized groups (quartiles), yet their total follow-up time was taken into account for the analyses. There were no missing data on exposures, outcomes or confounding variables. Effect estimates were only reported when at least 5 individuals developed the outcome.

Patient involvement

The Swedish patient organization for cancer of the esophagus, stomach, liver, and pancreas was involved in supporting the present study (www.palema.org). The development of the research question and outcome measures were informed by patients' priorities, experience, and preferences. The results will be disseminated to study participants by means of patient organizations. Patients are thanked in the acknowledgements.

Results

Among all 1,368,027 users of NSAIDs, there were 783,870 (57.3%) aspirin users, 566,209 (41.4%) non-selective NSAIDs users, and 17,948 (1.3%) COX-2 users (Table 1, Supplement 1). Aspirin users were more likely to be male (53.8%) and older than 70 years (54.9.2%), while non-selective NSAID users and COX-2 users were predominantly female (62.8% and 59.9%, respectively) and between 40 and 70 years of age (68.2% and 70.8%,

respectively). Use of PPIs was found in 25.6%, 26.2%, and 31.2% of the aspirin users, non-selective NSAIDs users, and COX-2 users, respectively; and use of statins in 55.2%, 13.7% and 14.4%, respectively. The majority of the population received their first prescription during the first half year of the study period (2005), 54.9% of aspirin users, and 42.5% of non-selective NSAIDs users (Supplement 2).

Aspirin

As presented in Table 1, 10.969 (1.40%) aspirin users developed some type of gastrointestinal cancer during the follow-up. The most common cancer sites were colorectal (n=6,919; 0.88%), gastric (n=1,079; 0.14%), and pancreatic (n=1,114; 0.14%). There was no association with gastrointestinal cancer based on the overall SIRs for aspirin users (SIR=1.02, 95% CI 1.00-1.04) (Table 2). Shorter duration of use (<5.5 years) seemed to be associated with an increased risk for all gastro-intestinal cancers. Yet, longer duration of aspirin use was followed by a decreased SIR for gastrointestinal cancer (SIR=0.31, 95% CI 0.30-0.33 for those with an estimated use between 5.5-7.7 years, and SIR=0.37, 95%CI 0.35-0.40 for >7.7 years) (Table 3) and long-term aspirin users had clearly decreased SIRs for each gastrointestinal cancer type (Table 3). The subgroup analyses including only the low-dosage aspirin users (N=668,305, 85.3% of the aspirin cohort) showed lower SIRs for all cancer locations, with significantly reduced risks for all locations except for oesophageal, gastric and liver cancer (Supplement 3).

Non-selective NSAIDs

Table 1 shows that 3,428 (0.61%) of the non-selective NSAID users developed cancer, mainly colorectal (n=2,017; 0.36%), pancreatic (n=490; 0.09%), and gastric cancers (n=260; 0.05%). Overall, there was a decreased risk of gastrointestinal cancer (SIR=0.79, 95%CI 0.77-0.82), and also for gastric (SIR=0.70, 95% CI 0.62-0.80), colorectal (SIR=0.74, 95% CI 0.71-0.77) and oesophageal (SIR=0.75, 95% CI 0.63-0.89) cancers analysed separately (and their main histological subtypes) (Table 2). There was no evidence of decreased SIRs for the other types of gastrointestinal cancer types, although the effect sizes indicated a decreased SIR of small bowel and liver cancer. Longer duration of use of non-selective NSAIDs was associated with a decreased gastrointestinal cancer risk for all anatomical locations (Table 3).

Selective COX-2 inhibitors

Overall, 100 (0.56%) COX-2 users developed some type of gastrointestinal cancer, predominantly colorectal (n=60; 0.33%), pancreatic (n=13; 0.07%), gastric (n=7; 0.04%), and oesophageal cancers (n=7; 0.04%). There was some evidence for a decreased risk of gastrointestinal cancer overall (SIR=0.89, 95% CI 0.73-1.09), although not statistically significant. None of the sub-analyses showed strong evidence for an association (Supplement 3).

Relatively selective COX-2 inhibitors

Among the non-selective NSAIDs users, 7,609 individuals used relatively selective COX-2 inhibitors, of whom 74 (0.01%) developed cancer. There was

no evidence for an association with any of the gastrointestinal cancer locations (Supplement 3).

Aspirin with PPIs or statins

Users of aspirin with concomitant use of PPIs had higher SIRs for all gastrointestinal cancers compared to those not using PPIs, with all SIRs indicating an increased risk except for gallbladder cancer (Table 4). The SIRs were especially increased for gastric cancer (SIR=1.89; 95% CI 1.73-2.06) and oesophageal cancer (SIR=1.94; 95% CI 1.71-2.20). When using Poisson regression to compare aspirin users using PPIs directly with aspirin users not using PPIs (instead of using the background population as reference), the risk was increased for all gastrointestinal cancers (IRR=1.19, 95% CI 1.11-1.26), with significantly increased risks for oesophageal, gastric, small bowel, liver and pancreatic cancer (Supplement 4).

Among aspirin users exposed to statins, the SIRs were close to unity for each anatomical location (Table 4). When aspirin users using statins were directly compared with aspirin users not using statins, risks were decreased for all gastrointestinal cancers (IRR=0.81, 95% CI 0.77-0.85), with significant decreases for all cancer locations except for colorectal and pancreatic cancer (Supplement 4).

Non-selective NSAIDs with PPIs or statins

In users of non-selective NSAIDs on therapy with PPIs, the SIRs were increased for all gastrointestinal cancer types (and again higher than among those not using PPIs), except for colorectal cancer (Table 4). When users of

non-selective NSAIDs using PPIs were directly compared with those not using PPIs, risks were increased for all gastrointestinal cancers (IRR=1.61, 95% CI 1.49-1.74), and each individual cancer location except for gallbladder cancer (Supplement 4). Among non-selective NSAIDs users using statins, the SIRs were lower than among all users of non-selective NSAIDs, and significantly reduced for oesophageal, gastric and colorectal cancer. When users of non-selective NSAIDs using statins were directly compared with those not using statins, risks were decreased for all gastrointestinal cancers (IRR=0.86, 95% CI 0.76-0.96), yet not significant for the individual cancer locations (Supplement 4).

Discussion

This study on contemporary use of NSAIDs showed a decreased risk of all types of gastrointestinal cancer among long-term users of aspirin (>5.5 years) and non-selective NSAIDs users even for shorter duration of use (>0.7 years). Long-term users of non-selective NSAIDs were at a particularly decreased risk for gastric, oesophageal, and colorectal cancers. These seemingly protective associations might be counteracted by concomitant PPI therapy, and enhanced by concomitant statin use.

The main strengths of this study are the population-based design and large sample size, including all adults residing in Sweden during the study period, which enabled separate analyses for contemporary use of different types of NSAIDs, and evaluation of less common types of gastrointestinal cancer which could not be assessed previously because of insufficient power, in

particular for non-aspirin NSAIDs. Other advantages include the complete follow-up and accurate censoring for mortality. The data on the exposures (medications) and outcomes (gastrointestinal cancers) were highly accurate due to the validity and completeness of the Swedish registries, eliminating recall bias.

Although our findings for aspirin are largely consistent with the literature, that the protective effect is only seen after 5 years, reverse causation, confounding and/or bias appear to influence the aspirin analyses because of the apparent initial increased risk of cancer among short-term users. By excluding all individuals diagnosed with cancer within a year after enrolment, and only including those with a minimal accumulated duration of use of 6 months, the risk of reverse causation should be reduced. Yet, our results indicate that those with an estimated duration shorter than 5 years have an apparent increased risk, which might be because they take aspirin because of yet undiagnosed cancer-related pain or thrombotic events – indicating confounding by indication and reverse causation among the group with the shortest exposure time, an effect which could not have been detected in intervention trials or in case-control studies with a study-design-inherent more restrictive selection of study participants.[15 35] As previous studies reported, 15-20% of cancer patients have thrombotic complications during the course of the disease (often as early manifestation of an occult malignancy),[36] yet these complications (e.g. deep venous thrombosis) are more likely to be treated with anti-coagulants than aspirin. However, when only looking at those exclusively using low-dose aspirin for ≥180 days, i.e. the platelet aggregation

inhibitors, the protective effects were also visible in the overall analyses non taking into account duration, with SIR=0.86 (95%CI 0.85-0.88). This indicates that the apparent increased risks are mainly because of the small group using aspirin as analgesic (high dose), which shows it is important to distinguish between both groups of aspirin-use. Reverse causality seems to be less of a problem for other NSAIDs users, although these may be used as analgesics.[37] Yet, individuals using NSAIDs may be at a lower a-priori risk of developing gastro-intestinal cancer, because individuals with upper gastro-intestinal symptoms are less likely to be chronic NSAIDs users due to the risk of gastro-intestinal side-effects.

Especially for aspirin users (with a high cardiovascular mortality, higher average age than NSAIDs users and more chronic comorbidties), death is a competing risk for the development of cancer, reducing the number at risk to develop cancer. Therefore, we censored follow-up time at time of death. In this cohort the standardised mortality risks were 9.64 (95%CI 9.60-9.69) for aspirin users and 2.08 (95% CI 2.05-2.11) for non-selective non-aspirin NSAIDs users indeed showing a higher risk of death competing with the risk of cancer, leading to an overestimation of the protective effect in particular among aspirin users

Another limitation is potential confounding, e.g. by socio-economic status, dietary factors, obesity, tobacco smoking, and alcohol consumption, which could not be taken into account since such information was not available for the total background population. However, we adjusted for age, sex and calendar period. Cancer-type specific confounders and their treatment such

as *Helicobacter pylori for gastric cancer*, hepatitis B/C infection for liver cancer and chronic inflammatory diseases such as inflammatory bowel disease for bowel cancer and pancreatitis for pancreatic cancer, may also have contributed to the risk of cancer and timing of diagnosis. We may have incomplete exposure ascertainment (and underestimation of duration of use) for part of our cohort since no information was available on prescriptions before July 2005 or over-the-counter use. Yet, potential long-term (protective) effects may be expected to decrease gradually yet significantly after treatment cessation, reducing the potential effect of misclassification on our results due to exposure before 2005. We used the minimal exposure criterion of 180 days to exclude occasional users who are more likely to obtain their NSAIDs over-the-counter, so at a higher price. We did not have data on used daily dosage or duration of use, and used a proxy variable for duration based on accumulation of the average DDDs per package. This explains why some aspirin users had an estimated exposure time longer than the duration of follow-up, indicating a high daily dose. The high variability in actual and estimated administered dosage also hindered assessment of recency of use. Some previous studies subdivided aspirin use into “low dose” and “high dose” based on prescribed dosages (e.g. <75 mg/day[38] or <100 mg/day[14]), but since we did not have information on the number of prescribed pills per day, and different dosages could have been prescribed during the study period, we used the definition based on ATC coding and assessed the estimated duration of use, with the additional advantage that the low-dose aspirin was only available on prescription. This should also be a more accurate reflection of duration of use than the number of prescriptions.[9] In our study, the DDD

per package could range from <5 to 500 (for other NSAIDs) or 1000 (for aspirin), which illustrates the variation between prescriptions. Since 1.4 million individuals were exposed to NSAIDs (≥180 days), i.e. one fifth of the adult population in Sweden, our results are likely to be diluted since we compared them with the total background population. Yet, despite this dilution the associations among long-term users were strongly decreased.

Compared to previous studies, this study was better powered to separately analyses different gastrointestinal cancers and types of NSAIDs.[39] The above mentioned meta-analysis[15] identified only 2 cohort studies including over 100,000 individuals assessing colorectal cancer risk among aspirin-users.[40 41] Even our exposed groups for aspirin and non-selective NSAIDs alone were 5-7 times larger than earlier large studies. The decrease in gastrointestinal cancer risk became evident only after longer exposure, which has also been shown in previous research,[15 42] and is biologically plausible given the expected time latency for (hindering) cancer progression.

The higher risk among aspirin and other NSAID users also using PPIs should be interpreted with some caution. PPIs are often prescribed for gastroesophageal reflux and peptic ulcers, which are risk factors for oesophageal and gastric cancer, respectively. Therefore, a higher cancer risk was expected for those locations, yet not for the other gastrointestinal cancer types. PPIs can also be used to prevent peptic ulcers in users of aspirin and other NSAIDs, usually in individuals without any gastro-intestinal morbidity. Two other studies of our group based on the same source cohort,[23 25]

investigated the risk of gastric and oesophageal cancer among PPI maintenance users, which suggested an increased risk in all indication groups for PPI (including those without gastrointestinal symptoms, and aspirin/NSAID users); which also supports a potential independent role for PPI in carcinogenesis as also suggested recently by other groups.[43 44] Together with a potential increased risk of mortality related to long-term PPI use,[45] we believe a more careful approach should be considered when prescribing PPIs to prevent gastrointestinal complications in long-term NSAIDs users. Yet, the risk for gastrointestinal complications such as bleeding should be assessed on an individual bases based on other research investigating shorter-term effects.[46] Before considering implementing aspirin or other NSAIDs as wide-spread intervention, safety, in particular considering long-term use, needs to be considered, with previous research tending towards a “favourable benefit harm-profile” despite an excess risk of bleeding.[47]

To conclude, this large Swedish nationwide and population-based cohort study on contemporary and long-term use of NSAIDs indicates a strongly protective effect of long-term use of both (low-dose) aspirin and other non-selective NSAIDs on gastrointestinal cancer development.

Acknowledgements: We are grateful to all thousands of patients, physicians and healthcare staff members who contributed to the data collection, and to the Swedish National Board of Health and Welfare that collected the data.

Authors' contributions: NB is the submission guarantor. NB and JL had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. NB conducted and is responsible for the data-analysis. Literature search: NB; Design of the study: both authors; Data collection and preparation for analyses: NB; Data analysis: NB; Data interpretation: both authors; Writing of first draft: NB, revised and approved by both authors.

Funding: This work was supported by SFO epidemiology (Karolinska Institutet, junior investigator award NB), Swedish Research Council (839-2008-7496), Swedish Cancer Society (CAN 2015/460). These funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Competing interests: none

Data sharing statement: We are willing to share data upon request after ethics approval has been approved by the relevant committee and the governmental agencies that maintain the data.

References

1. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;**357**(9255):539-45 doi: 10.1016/s0140-6736(00)04046-0[published Online First: Epub Date]|.
2. Simon LS, Yocum D. New and future drug therapies for rheumatoid arthritis. Rheumatology (Oxford) 2000;**39 Suppl 1**:36-42
3. Yang M, Wang HT, Zhao M, et al. Network Meta-Analysis Comparing Relatively Selective COX-2 Inhibitors Versus Coxibs for the Prevention of NSAID-Induced Gastrointestinal Injury. Medicine 2015;**94**(40):e1592 doi: 10.1097/MD.0000000000001592[published Online First: Epub Date]|.
4. Sjodahl R. Nonsteroidal anti-inflammatory drugs and the gastrointestinal tract. Extent, mode, and dose dependence of anticancer effects. Am J Med 2001;**110**(1a):66s-69s
5. Huntjens DR, Danhof M, Della Pasqua OE. Pharmacokinetic-pharmacodynamic correlations and biomarkers in the development of COX-2 inhibitors. Rheumatology (Oxford) 2005;**44**(7):846-59 doi: 10.1093/rheumatology/keh627[published Online First: Epub Date]|.
6. Bjarnason I, Thjodleifsson B. Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs: the effect of nimesulide compared with naproxen on the human gastrointestinal tract. Rheumatology (Oxford) 1999;**38 Suppl 1**:24-32
7. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;**375**(26):2519-29 doi: 10.1056/NEJMoa1611593[published Online First: Epub Date]|.
8. Bakhriansyah M, Souverein PC, de Boer A, et al. Gastrointestinal toxicity among patients taking selective COX-2 inhibitors or conventional NSAIDs, alone or combined with proton pump inhibitors: a case-control study. Pharmacoepidemiol Drug Saf 2017 doi: 10.1002/pds.4183[published Online First: Epub Date]|.

9. Capurso G, Schunemann HJ, Terrenato I, et al. Meta-analysis: the use of non-steroidal anti-inflammatory drugs and pancreatic cancer risk for different exposure categories. Aliment Pharmacol Ther 2007;**26**(8):1089-99 doi: 10.1111/j.1365-2036.2007.03495.x[published Online First: Epub Date]|.
10. Tian W, Zhao Y, Liu S, et al. Meta-analysis on the relationship between nonsteroidal anti-inflammatory drug use and gastric cancer. Eur J Cancer Prev 2010;**19**(4):288-98 doi: 10.1097/CEJ.0b013e328339648c[published Online First: Epub Date]|.
11. Yang P, Zhou Y, Chen B, et al. Aspirin use and the risk of gastric cancer: a meta-analysis. Dig Dis Sci 2010;**55**(6):1533-9 doi: 10.1007/s10620-009-0915-0[published Online First: Epub Date]|.
12. Ye X, Fu J, Yang Y, et al. Dose-risk and duration-risk relationships between aspirin and colorectal cancer: a meta-analysis of published cohort studies. PLoS One 2013;**8**(2):e57578 doi: 10.1371/journal.pone.0057578[published Online First: Epub Date]|.
13. Ye X, Fu J, Yang Y, et al. Frequency-risk and duration-risk relationships between aspirin use and gastric cancer: a systematic review and meta-analysis. PLoS One 2013;**8**(7):e71522 doi: 10.1371/journal.pone.0071522[published Online First: Epub Date]|.
14. Cui XJ, He Q, Zhang JM, et al. High-dose aspirin consumption contributes to decreased risk for pancreatic cancer in a systematic review and meta-analysis. Pancreas 2014;**43**(1):135-40 doi: 10.1097/MPA.0b013e3182a8d41f[published Online First: Epub Date]|.
15. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 2012;**13**(5):518-27 doi: 10.1016/S1470-2045(12)70112-2[published Online First: Epub Date]|.
16. Sutcliffe P, Connock M, Gurung T, et al. Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews. Health Technol Assess 2013;**17**(43):1-253 doi: 10.3310/hta17430[published Online First: Epub Date]|.

17. Cheung KS, Chan EW, Wong AYS, et al. Aspirin and Risk of Gastric Cancer After Helicobacter pylori Eradication: A Territory-Wide Study. LID - 10.1093/jnci/djx267 [doi]. (1460-2105 (Electronic))
18. Niikura R, Hayakawa Y, Hirata Y, et al. Distinct chemopreventive effects of aspirin in diffuse and intestinal-type gastric cancer. LID - canprevres.0276.2017 [pii] LID - 10.1158/1940-6207.CAPR-17-0276 [doi]. (1940-6215 (Electronic))
19. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. Gut 2016;**65**(5):740-8 doi: 10.1136/gutjnl-2015-310376[published Online First: Epub Date]|.
20. Alsalahi O, Dobrian AD. Proton Pump Inhibitors: The Culprit for Barrett's Esophagus? Front Oncol 2014;**4**:373 doi: 10.3389/fonc.2014.00373[published Online First: Epub Date]|.
21. Kia L, Kahrilas PJ. Therapy: Risks associated with chronic PPI use - signal or noise? Nat Rev Gastroenterol Hepatol 2016 doi: 10.1038/nrgastro.2016.44[published Online First: Epub Date]|.
22. Poulsen AH, Christensen S, McLaughlin JK, et al. Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. Br J Cancer 2009;**100**(9):1503-7 doi: 10.1038/sj.bjc.6605024[published Online First: Epub Date]|.
23. Brusselaers N, Engstrand L, Lagergren J. Maintenance proton pump inhibition therapy and risk of oesophageal cancer. Cancer epidemiology 2018;**53**:172-77 doi: 10.1016/j.canep.2018.02.004[published Online First: Epub Date]|.
24. Brusselaers N, Engstrand L, Lagergren J. PPI use and oesophageal cancer: What if the results are true? Cancer epidemiology 2018 doi: 10.1016/j.canep.2018.04.004[published Online First: Epub Date]|.
25. Brusselaers N, Wahlin K, Engstrand L, et al. Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden. BMJ Open 2017;**7**(10):e017739 doi: 10.1136/bmjopen-2017-017739[published Online First: Epub Date]|.
26. Ma Y, Brusselaers N. Maintenance use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) and prostate cancer risk. Prostate

Cancer Prostatic Dis 2017 doi: 10.1038/s41391-017-0021-x[published Online First: Epub Date]|.

27. Statistics Sweden - Statistical Database Population Statistics (accessed 06 April 2016) http://www.statistikdatabasen.scb.se/. Secondary Statistics Sweden - Statistical Database Population Statistics (accessed 06 April 2016) http://www.statistikdatabasen.scb.se/. http://www.statistikdatabasen.scb.se/.
28. Simin J, Tamimi R, Lagergren J, et al. Menopausal hormone therapy and cancer risk: An overestimated risk? Eur J Cancer 2017;**84**:60-68 doi: 10.1016/j.ejca.2017.07.012[published Online First: Epub Date]|.
29. Brusselaers N, Maret-Ouda J, Konings P, et al. Menopausal hormone therapy and the risk of esophageal and gastric cancer. Int J Cancer 2016 doi: 10.1002/ijc.30588[published Online First: Epub Date]|.
30. Sadr-Azodi O, Konings P, Brusselaers N. Menopausal hormone therapy and pancreatic cancer risk in women: a population-based matched cohort study. United European Gastroenterol J 2017;**5**(8):1123-28 doi: 10.1177/2050640617702060[published Online First: Epub Date]|.
31. Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 2009;**48**(1):27-33 doi: 902131375 [pii]

10.1080/02841860802247664[published Online First: Epub Date]|.

32. FASS (Farmacevtiska specialiteter i Sverige/ Farmaceutical specialities in Sweden), 2015.
33. Läkemedelsverket (Medical Products Agency): Over-the-counter (OTC). Secondary Läkemedelsverket (Medical Products Agency): Over-the-counter (OTC) 2016. https://lakemedelsverket.se/english/product/Medicinal-products/OTC/.
34. Breslow N, Day N. *Statistical Methods in Cancer Research: The design and analysis of cohort studies*. Lyon, 1987.
35. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 2010;**376**(9754):1741-50 doi: 10.1016/S0140-6736(10)61543-7[published Online First: Epub Date]|.

36. Kyriazi V, Theodoulou E. Assessing the risk and prognosis of thrombotic complications in cancer patients. Arch Pathol Lab Med 2013;**137**(9):1286-95 doi: 10.5858/arpa.2012-0490-RA[published Online First: Epub Date]|.
37. Mercadante S. The use of anti-inflammatory drugs in cancer pain. Cancer Treat Rev 2001;**27**(1):51-61 doi: 10.1053/ctrv.2000.0192[published Online First: Epub Date]|.
38. Din FV, Theodoratou E, Farrington SM, et al. Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. Gut 2010;**59**(12):1670-9 doi: 10.1136/gut.2009.203000[published Online First: Epub Date]|.
39. Bosetti C, Rosato V, Gallus S, et al. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol 2012;**23**(6):1403-15 doi: 10.1093/annonc/mds113[published Online First: Epub Date]|.
40. Jacobs EJ, Thun MJ, Bain EB, et al. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst 2007;**99**(8):608-15 doi: 10.1093/jnci/djk132[published Online First: Epub Date]|.
41. Smalley W, Ray WA, Daugherty J, et al. Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. Arch Intern Med 1999;**159**(2):161-6
42. Cao Y, Nishihara R, Wu K, et al. Population-wide Impact of Long-term Use of Aspirin and the Risk for Cancer. JAMA Oncol 2016;**2**(6):762-9 doi: 10.1001/jamaoncol.2015.6396[published Online First: Epub Date]|.
43. Cheung KS, Chan EW, Wong AYS, et al. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut 2018;**67**(1):28-35 doi: 10.1136/gutjnl-2017-314605[published Online First: Epub Date]|.
44. Niikura R, Hayakawa Y, Hirata Y, et al. Long-term proton pump inhibitor use is a risk factor of gastric cancer after treatment for Helicobacter pylori: a retrospective cohort analysis. Gut 2017 doi: 10.1136/gutjnl-2017-315710[published Online First: Epub Date]|.
45. Xie Y, Bowe B, Li T, et al. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States

veterans. BMJ Open 2017;**7**(6):e015735 doi: 10.1136/bmjopen-2016-015735[published Online First: Epub Date]|.

46. Li L, Geraghty OC, Mehta Z, et al. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017;**390**(10093):490-99 doi: 10.1016/s0140-6736(17)30770-5[published Online First: Epub Date]|.
47. Cuzick J, Thorat MA, Bosetti C, et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol 2015;**26**(1):47-57 doi: 10.1093/annonc/mdu225[published Online First: Epub Date]|.

Table 1: Characteristics of the study cohort on therapy with aspirin, selective cyclo-oxygenase-2 (COX-2) inhibitors, and non-selective non-steroidal anti-inflammatory drug (NSAIDs).

	Aspirin only	Non-selective non-aspirin NSAIDs	Selective COX-2 inhibitors
	Number (%)	*Number (%)*	*Number (%)*
Total	783,870	566,209	17,948
Sex			
Men	421,609 (53.8)	210,705 (37.2)	7,201 (40.1)
Women	362,261 (46.2)	355,504 (62.8)	10,747 (59.9)
Age at first prescription			
<40 years	12,189 (1.6)	110,592 (19.5)	2,720 (15.2)
40-49 years	32,743 (4.2)	125,977 (22.3)	3,849 (21.5)
50-59 years	108,683 (13.9)	146,981 (26.0)	4,941 (27.5)
60-69 years	200,154 (25.5)	112,682 (19.9)	3,914 (21.8)
≥70 years	430,101 (54.9)	69,977 (12.4)	2,524 (14.1)
Calendar period at first prescription			
2005-2006	557,023 (71.1)	387,443 (68.4)	10,393 (57.9)
2007-2009	156,790 (20.0)	145,208 (25.7)	5,500 (30.6)
2010-2012	70,057 (8.9)	33,558 (5.9)	2,055(11.5)
Proton pump inhibitors use (≥180 days)			
yes	200,828 (25.6)	148,586 (26.2)	5,602 (31.2)
no	583,042 (74.4)	417,623 (73.8)	12,346 (68.8)
Statins use (≥180 days)			
yes	432,996 (55.2)	77,514 (13.7)	2,589 (14.4)
no	350,874 (44.8)	488,695 (86.3)	15,359 (85.6)
Gastrointestinal cancer	10,969 (1.40)	3,428 (0.61)	100 (0.56)
Oesophageal cancer	539 (0.07)	134 (0.02)	7 (0.04)
Adenocarcinoma	319 (0.04)	75 (0.01)	4 (0.02)
Squamous cell carcinoma	203 (0.03)	50 (0.01)	2 (0.01)
Gastric cancer	1,079 (0.14)	260 (0.05)	7 (0.04)
Adenocarcinoma	949 (0.12)	212 (0.04)	3 (0.02)
Small bowel cancer	253 (0.03)	94 (0.02)	5 (0.03)
Carcinoid	122 (0.02)	43 (0.01)	2 (0.01)
Colorectal cancer	6,919 (0.88)	2,017 (0.36)	60 (0.33)
Adenocarcinoma	6,608 (0.84)	1,887 (0.33)	59 (0.33)
Liver cancer	645 (0.08)	232 (0.04)	3 (0.02)
Hepatocellular carcinoma	358 (0.05)	100 (0.02)	1 (0.01)
Cholangiocellular carcinoma	81 (0.01)	41 (0.01)	0 (0.00)
Gallbladder and biliary tract cancer	385 (0.05)	190 (0.03)	5 (0.03)
Adenocarcinoma	288 (0.04)	149 (0.03)	2 (0.01)
Pancreatic cancer	1,114 (0.14)	490 (0.09)	13 (0.07)
Adenocarcinoma	835 (0.11)	402 (0.07)	11 (0.06)

Other gastrointestinal cancer	35 (0.00)	11 (0.00)	0 (0.00)
Duration of follow-up in person-years			
Total	3,776,237	3,376,275	82,733
Mean (standard deviation)	4.82 (2.40)	5.96 (1.67)	4.61 (2.21)

Table 2: The risk of different types of gastrointestinal cancer (and the major histological subtype) among users of aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), expressed as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) and stratified by age and sex.

	Aspirin users (n=783,870)		Non-selective non-aspirin NSAIDs users (n=566,209)	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
Gastrointestinal cancer	**10,969**	**1.02 (1.00-1.04)**	**3,428**	**0.79 (0.77-0.82)**
Men	6,659	1.24 (1.21-1.27)	1,390	0.78 (0.74-0.82)
Women	4,310	0.99 (0.96-1.02)	2,038	0.81 (0.77-0.84)
18-39 years	3	-	14	0.59 (0.32-0.99)
40-49 years	20	0.70 (0.43-1.08)	116	0.67 (0.55-0.81)
50-59 years	408	1.13 (1.03-1.25)	423	0.61 (0.55-0.67)
60-69 years	2,286	1.13 (1.08-1.18)	1,074	0.71 (0.67-0.75)
≥70 years	8,252	0.99 (0.97-1.01)	1,801	0.94 (0.90-0.98)
Oesophageal cancer	**539**	**1.10 (1.01-1.19)**	**134**	**0.75 (0.63-0.89)**
Adenocarcinoma	319	1.17 (1.04-1.30)	75	0.81 (0.64-1.01)
Squamous cell carcinoma	203	1.06 (0.92-1.22)	50	0.66 (0.49-0.87)
Men	415	1.09 (0.99-1.20)	90	0.88 (0.63-0.97)
Women	124	1.12 (0.93-1.33)	44	0.68 (0.49-0.91)
18-39 years	0	-	0	-
40-49 years	1	-	5	0.87 (0.28-2.03)
50-59 years	21	0.99 (0.61-1.51)	18	0.58 (0.34-0.92)
60-69 years	164	1.35 (1.15-1.57)	47	0.65 (0.48-0.86)
≥70 years	353	1.02 (0.92-1.13)	64	0.92 (0.71-1.18)
Gastric cancer	**1,079**	**1.08 (1.01-1.14)**	**260**	**0.70 (0.62-0.80)**
Adenocarcinoma	949	1.07 (1.00-1.14)	212	0.66 (0.58-0.76)
Men	714	1.08 (1.00-1.16)	128	0.72 (0.60-0.85)
Women	365	1.08 (0.97-1.19)	132	0.69 (0.58-0.82)
18-39 years	0	-	1	-
40-49 years	3	-	13	0.71 (0.38-1.22)
50-59 years	51	1.48 (1.10-1.94)	37	0.61 (0.43-0.85)
60-69 years	208	1.20 (1.04-1.37)	73	0.61 (0.48-0.77)
≥70 years	817	1.03 (0.96-1.11)	136	0.81 (0.68-0.95)
Small bowel cancer	**253**	**1.05 (0.93-1.19)**	**94**	**0.84 (0.68-1.02)**
Carcinoid	122	1.11 (0.92-1.32)	43	0.84 (0.61-1.13)
Men	150	1.05 (0.89-1.23)	34	0.72 (0.50-1.00)
Women	103	1.06 (0.86-1.28)	60	0.93 (0.71-1.19)
18-39 years	0	-	1	-
40-49 years	1	-	3	-

50-59 years	18	1.53 (0.91-2.41)	18	0.77 (0.46-1.22)
60-69 years	64	1.16 (0.89-1.48)	33	0.81 (0.56-1.14)
≥70 years	170	0.99 (0.85-1.15)	39	0.98 (0.69-1.34)
Colorectal cancer	**6,919**	**1.00 (0.98-1.03)**	**2,017**	**0.74 (0.71-0.77)**
Adenocarcinoma	6,608	1.00 (0.80-1.03)	1,887	0.74 (0.70-0.77)
Men	4,105	1.03 (1.00-1.06)	793	0.73 (0.68-0.79)
Women	2,814	0.97 (0.93-1.00)	1,224	0.74 (0.70-0.78)
18-39 years	2	-	10	0.61 (0.29-1.13)
40-49 years	9	0.52 (0.24-0.98)	51	0.47 (0.35-0.62)
50-59 years	241	1.16 (1.02-1.31)	232	0.55 (0.48-0.63)
60-69 years	1,268	1.05 (0.99-1.11)	600	0.66 (0.60-0.71)
≥70 years	5,399	0.99 (0.96-1.02)	1,124	0.88 (0.83-0.94)
Liver cancer	**645**	**1.11 (1.03-1.20)**	**232**	**0.96 (0.84-1.09)**
Hepatocellular carcinoma	358	1.13 (1.02-1.25)	100	0.83 (0.77-1.01)
Cholangiocellular carcinoma	81	1.14 (0.91-1.42)	41	1.10 (0.79-1.49)
Men	449	1.12 (1.02-1.23)	130	1.00 (0.84-1.19)
Women	196	1.09 (0.94-1.26)	102	0.91 (0.74-1.10)
18-39 years	0	-	3	-
40-49 years	4	-	10	0.95 (0.46-1.75)
50-59 years	32	1.04 (0.71-1.47)	44	0.90 (0.65-1.21)
60-69 years	182	1.36 (1.17-1.57)	90	0.99 (0.79-1.21)
≥70 years	427	1.03 (0.94-1.14)	85	0.95 (0.76-1.17)
Gallbladder and biliary tract cancer	**385**	**0.92 (0.83-1.01)**	**190**	**1.03 (0.89-1.19)**
Adenocarcinoma	288	0.93 (0.82-1.04)	149	1.07 (0.90-1.25)
Men	181	1.00 (0.86-1.15)	50	0.98 (0.73-1.29)
Women	204	0.85 (0.74-0.80)	140	1.05 (0.88-1.24)
18-39 years	0	-	1	-
40-49 years	0	-	7	0.97 (0.39-2.00)
50-59 years	6	0.52 (.19-1.13)	12	0.46 (0.24-0.80)
60-69 years	91	1.31 (1.05-1.60)	63	1.00 (0.77-1.28)
≥70 years	288	0.85 (0.76-0.96)	107	1.23 (1.00-1.48)
Pancreatic cancer	**1,114**	**1.04 (0.98-1.11)**	**490**	**1.00 (0.92-1.10)**
Adenocarcinoma	835	1.00 (0.93-1.07)	402	1.02 (0.92-1.13)
Men	629	1.07 (0.99-1.16)	163	0.89 (0.76-1.03)
Women	485	1.01 (0.92-1.11)	327	1.08 (0.96-1.20)
18-39 years	1	-	1	-
40-49 years	3	-	26	1.65 (1.08-2.42)
50-59 years	37	0.91 (0.64-1.25)	68	0.86 (0.67-1.09)
60-69 years	307	1.19 (1.06-1.33)	174	0.85 (0.73-0.99)
≥70 years	766	1.00 (0.93-1.07)	221	1.18 (1.03-1.35)

Table 3: The risk of gastrointestinal cancer among aspirin and non-aspirin non-steroidal anti-inflammatory drug (NSAID) users, by estimated duration of use, expressed as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs).

	Aspirin only (n=783,870)			Non-selective non-aspirin NSAIDs (n=566,209)		
	Categories (quartiles)	*Number of cases*	*SIRs (95% CI)*	*Categories (quartiles)*	*Number of cases*	*SIRs (95% CI)*
Gastrointestinal cancer						
	0.5-2.5 years	4,158	2.77 (2.69-2.85)	*0.5-0.7 years*	865	1.00 (0.93-1.06)
	2.5-5.5 years	4,532	1.83 (1.77-1.88)	*0.7-1.1 years*	832	0.92 (0.86-0.98)
	5.5-7.7 years	1,310	0.31 (0.30-0.33)	*1.1-2.1 years*	977	0.86 (0.80-0.91)
	>7.7 years	969	0.37 (0.35-0.40)	*>2.1 years*	754	0.54 (0.50-0.58)
Oesophageal cancer						
	0.5-2.5 years	204	2.91 (2.52-3.33)	*0.5-0.7 years*	35	0.93 (0.65-1.29)
	2.5-5.5 years	216	1.83 (1.60-2.09)	*0.7-1.1 years*	32	0.84 (0.57-1.18)
	5.5-7.7 years	61	0.31 (0.24-0.40)	*1.1-2.1 years*	43	0.91 (0.66-1.23)
	>7.7 years	58	0.56 (0.42-0.72)	*>2.1 years*	23	0.41 (0.26-0.61)
Gastric cancer						
	0.5-2.5 years	61	2.89 (2.62-3.19)	*0.5-0.7 years*	55	0.73 (0.55-0.95)
	2.5-5.5 years	466	2.00 (1.82-2.19)	*0.7-1.1 years*	61	0.78 (0.60-1.01)
	5.5-7.7 years	99	0.26 (0.21-0.31)	*1.1-2.1 years*	80	0.82 (0.65-1.02)
	>7.7 years	110	0.45 (0.37-0.55)	*>2.1 years*	64	0.54 (0.42-0.69)
Small bowel cancer						
	0.5-2.5 years	96	2.78 (2.25-3.39)	*0.5-0.7 years*	22	0.94 (0.59-1.43)
	2.5-5.5 years	109	1.94 (1.59-2.33)	*0.7-1.1 years*	20	0.83 (0.51-1.29)
	5.5-7.7 years	26	0.28 (0.18-0.41)	*1.1-2.1 years*	25	0.85 (0.55-1.25)
	>7.7 years	22	0.39 (0.25-0.60)	*>2.1 years*	27	0.76 (0.50-1.11)
Colorectal cancer						
	0.5-2.5 years	2,658	2.78 (2.67-2.88)	*0.5-0.7 years*	540	0.99 (0.91-1.08)
	2.5-5.5 years	2,844	1.79 (1.73-1.86)	*0.7-1.1 years*	489	0.86 (0.78-0.94)

	5.5-7.7 years	813	0.31 (0.29-0.33)	*1.1-2.1 years*	565	0.78 (0.72-0.85)
	>7.7 years	604	0.36 (0.33-0.39)	*>2.1 years*	423	0.47 (0.43-0.52)
Liver cancer						
	0.5-2.5 years	222	2.63 (2.30-3.00)	*0.5-0.7 years*	63	1.23 (0.95-1.57)
	2.5-5.5 years	272	1.96 (1.74-2.21)	*0.7-1.1 years*	53	1.02 (0.76-1.33)
	5.5-7.7 years	100	0.44 (0.35-0.53)	*1.1-2.1 years*	70	1.10 (0.86-1.39)
	>7.7 years	51	0.40 (0.30-0.53)	*>2.1 years*	46	0.61 (0.45-0.81)
Gallbladder and biliary tract cancer						
	0.5-2.5 years	137	2.36 (1.98-2.79)	*0.5-0.7 years*	42	1.17 (0.85-1.58)
	2.5-5.5 years	143	1.52 (1.28-1.79)	*0.7-1.1 years*	51	1.34 (1.00-1.76)
	5.5-7.7 years	61	0.39 (0.30-.50)	*1.1-2.1 years*	52	1.06 (0.79-1.39)
	>7.7 years	44	0.40 (0.29-0.53)	*>2.1 years*	45	0.73 (0.53-0.98)
Pancreatic cancer						
	0.5-2.5 years	424	2.79 (2.53-3.06)	*0.5-0.7 years*	107	1.09 (0.90-1.32)
	2.5-5.5 years	467	1.87 (1.71-2.06)	*0.7-1.1 years*	123	1.20 (1.00-1.43)
	5.5-7.7 years	149	0.36 (0.30-0.42)	*1.1-2.1 years*	136	1.05 (0.88-1.25)
	>7.7 years	74	0.28 (0.23-0.37)	*>2.1 years*	124	0.78 (0.65-0.93)

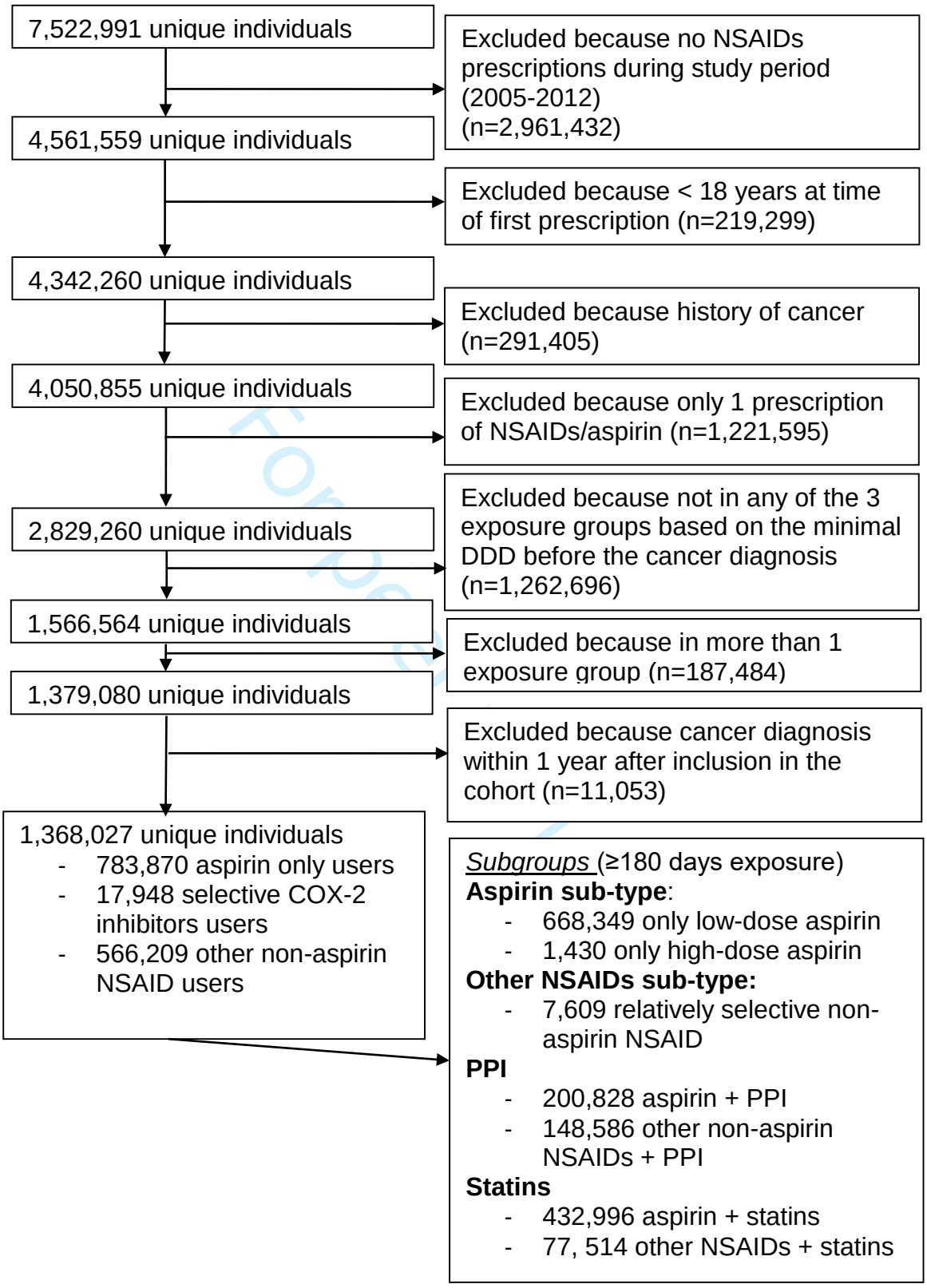
Table 4: The risk of gastrointestinal cancer among aspirin and non-selective non-aspirin non-steroidal anti-inflammatory drug (NSAID) users, stratified by additional use of proton pump inhibitors (PPIs) or statins compared to the total Swedish background population, expressed as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs).

	Aspirin users (n=783,870)		Aspirin with PPI (n=200,828)		Aspirin with statins (n=432,996)	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
All gastrointestinal cancer	10,969	1.02 (1.00-1.04)	3,617	1.25 (1.21-2.29)	6,210	0.99 (0.96-1.01)
Oesophageal cancer	539	1.10 (1.01-1.19)	247	1.94 (1.71-2.20)	299	0.98 (0.87-1.09)
Gastric cancer	1,079	1.08 (1.01-1.14)	509	1.89 (1.73-2.06)	619	1.05 (0.98-1.13)
Small bowel cancer	253	1.05 (0.93-1.19)	107	1.67 (1.37-2.01)	139	0.97 (0.81-1.14)
Colorectal cancer	6,919	1.00 (0.98-1.03)	2,004	1.07 (1.02-1.12)	3,893	0.97 (0.94-1.00)
Liver cancer	645	1.11 (1.03-1.20)	231	1.52 (1.33-1.73)	351	0.99 (0.89-1.10)
Gallbladder and biliary tract cancer	385	0.92 (0.83-1.01)	117	1.00 (0.82-1.19)	212	0.90 (0.78-1.03)
Pancreatic cancer	1,114	1.04 (0.98-1.11)	391	1.36 (1.23-1.50)	678	1.07 (0.99-2.15)

	Non-aspirin NSAIDs users (n=567,569)		Non-selective non-aspirin with PPI (n=148,586)		Non-selective non-aspirin with statins (n=77,514)	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
All gastrointestinal cancer	3,428	0.79 (0.77-0.82)	1,360	1.08 (1.02-1.13)	625	0.71 (0.65-0.76)
Oesophageal cancer	134	0.75 (0.63-0.89)	67	1.36 (1.05-1.73)	24	0.64 (0.41-0.95)
Gastric cancer	260	0.70 (0.62-0.80)	156	1.47 (1.25-1.72)	44	0.58 (0.42-0.78)
Small bowel cancer	94	0.84 (0.68-1.02)	45	1.39 (1.02-1.87)	14	0.64 (0.35-1.07)
Colorectal cancer	2,017	0.74 (0.71-0.77)	694	0.86 (0.80-0.93)	380	0.68 (0.61-0.75)
Liver cancer	232	0.96 (0.84-1.09)	102	1.51 (1.23-1.83)	38	0.78 (0.55-1.07)
Gallbladder and biliary tract cancer	190	1.03 (0.89-1.19)	68	1.21 (0.94-1.53)	29	0.76 (0.51-1.10)
Pancreatic cancer	490	1.00 (0.92-1.10)	222	1.55 (1.35-1.76)	93	0.92 (0.75-1.13)

Online Supplement 1

Description of original cohort, the “Chemoprevention of Cancer” cohort, and flow-chart describing the selection of the study cohort.



Abbreviations: COX, cyclooxygenase; DDD, defined daily dosage; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors

This cohort included all individuals residing in Sweden who received at least one dispensed prescription of one of the following commonly prescribed drugs between July 1, 2005 and December 31, 2014 (with corresponding ATC codes) with follow-up for cancer until December 2012: sex hormones (G03), drugs for peptic ulcers and gastro-esophageal reflux disease (A02B), acetylsalicylic acid (B01AC06, N02BA), non-steroidal anti-inflammatory drugs (M01A), HMG CoA reductase inhibitors (C10AA), drugs affecting bone structure and mineralization, (M05B), and antibiotics (J01AA, J01CA04, J01FA, J01MA, J01XD, J01XE, J04AB04). This cohort included approximately 85% of all Swedish residents, with especially high coverage of adults.

Supplement 2: Year of first prescription among aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) users during the study period.

	Aspirin	Non-aspirin NSAIDs
	N (%)	*N (%)*
2005	430,391 (54.9)	240,848 (42.5)
2006	79,356 (10.1)	143,805 (25.4)
2007	60,071 (7.7)	71,053 (12.6)
2008	55,527 (7.1)	46,013 (8.1)
2009	49,885 (6.4)	29,814 (5.3)
2010	43,290 (5.5)	18,957 (3.4)
2011	38,415 (4.9)	11,736 (2.1)
2012	26,935 (3.4)	3,983 (0.7)
Total	783,87	566,209

Supplement 3: The risk of gastrointestinal cancer among maintenance users of cyclo-oxygenase-2 (COX-2) selective inhibitors and relatively selective COX-2 inhibitors, and low-dose aspirin users, presented as standardized incidence ratios (SIRs) and 95% confidence intervals (CIs).

	COX-2 selective inhibitors maintenance users (n=17,948)		**Relatively selective COX-2 inhibitors maintenance users (n=7,609)**		**Low-dose aspirin (n=668,305)**	
	Number of cases	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*	*Number of cases*	*SIRS (95% CI)*
Gastrointestinal cancer	100	0.89 (0.73-1.09)	74	0.97 (0.76-1.21)	9,996	0.86 (0.85-0.88)
Oesophageal cancer	7	1.49 (0.60-3.07)	1	-	493	0.99 (0.91-1.08)
Gastric cancer	7	0.74 (0.30-1.52)	4	-	986	0.94 (0.88-1.00)
Small bowel cancer	5	1.72 (0.55-4.00)	3	-	224	0.84 (0.74-0.96)
Colorectal cancer	60	0.85 (0.65-1.09)	50	1.02 (0.76-1.35)	6,338	0.85 (0.83-0.88)
Liver cancer	3	-	3	-	592	0.97 (0.89-1.05)
Gallbladder and biliary tract cancer	5	1.05 (0.34-2.44)	3	-	344	0.74 (0.66-0.82)
Pancreatic cancer	13	1.02 (0.54-1.74)	10	1.15 (0.55-2.12)	990	0.80 (0.75-0.85)

Supplement 4: The risk of gastrointestinal cancer among aspirin and non-selective non-aspirin non-steroidal anti-inflammatory drug (NSAID) users comparing users with non-users of additional proton pump inhibitors (PPI) or statins, calculated with Poisson Regression models and expressed as incidence rate ratios (IRR) and 95% confidence intervals (CIs).

	Aspirin with PPI vs. without	Aspirin with statin vs. without	Non-selective non-aspirin NSAIDs with PPI vs. without	Non-selective non-aspirin NSAIDs with statins vs. without
	IRR (95% CI)	*IRR (95% CI)*	*IRR (95% CI)*	*IRR (95% CI)*
All gastrointestinal cancer	1.19 (1.11-1.26)	0.81 (0.77-0.85)	1.61 (1.49-1.74)	0.86 (0.76-0.96)
Oesophageal cancer	2.16 (1.67-2.80)	0.59 (0.47-0.75)	2.58 (1.77-3.75)	0.65 (0.32-1.31)
Gastric cancer	2.26 (1.88-2.71)	0.81 (0.69-0.96)	3.68 (2.80-4.83)	0.62 (0.34-1.11)
Small bowel cancer	1.65 (1.12-2.42)	0.65 (0.47-0.90)	2.20 (1.41-3.42)	0.62 (0.26-1.47)
Colorectal cancer	0.98 (0.90-1.06)	0.85 (0.80-1.90)	1.30 (1.17-1.44)	0.94 (0.81-1.08)
Liver cancer	1.56 (1.23-1.99)	0.64 (0.53-0.78)	2.12 (1.59-2.82)	0.79 (0.49-1.27)
Gallbladder and biliary tract cancer	0.70 (0.49-1.02)	0.67 (0.52-0.86)	1.28 (0.92-1.77)	0.67 (0.40-1.11)
Pancreatic cancer	1.32 (1.08-1.62)	0.90 (0.77-1.04)	1.88 (1.54-2.30)	0.78 (0.55-1.09)

Adjusted for age at first prescription, sex, and interaction between PPI and statins

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

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p 1 & 3 (abstract & title)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p 5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	p 6
Methods			
Study design	4	Present key elements of study design early in the paper	p 7-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p 7-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	p 7-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p 7-10 + appendix
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	p 7-10
Bias	9	Describe any efforts to address potential sources of bias	p 7-10
Study size	10	Explain how the study size was arrived at	Fig 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p 7-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p 9-10
		(*b*) Describe any methods used to examine subgroups and interactions	p 9-10
		(*c*) Explain how missing data were addressed	p 9-10
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
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	Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p 11, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 1-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	Tables 2-4

		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	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p 11-13, appendix
Discussion			
Key results	18	Summarise key results with reference to study objectives	p 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	p 14-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p 14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	p 14-17
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	p 3, p 17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.