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

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

Running title: NSAIDs and gastrointestinal cancer prevention

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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

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3 were using PPIs, had higher risks for all gastrointestinal cancer types; and
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5 lower risk if using statins.
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7 **Conclusion:** Long-term use of (low-dose) aspirin and non-selective NSAIDs
8
9 was associated with a decreased risk of all gastrointestinal cancer types.
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13 **Key words:** gastro-intestinal cancer, chemoprevention, non-steroidal anti-
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15 inflammatory drugs, aspirin, coxibs, cancer, pharmaco-epidemiology.
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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

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3 gastrointestinal toxicity, yet a higher risk of cardiovascular morbidity for COX-
4 2 selective inhibitors compared to nonselective COX-inhibitors.[3 7] [8] Some
5 of the older NSAIDs are “relatively selective COX-2 inhibitors”, i.e.
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8 nabumetone, meloxicam, etodolac and nimesulide.[3]
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11 However, epidemiological evidence to support a chemopreventive effect is still
12
13 limited, mainly because large numbers are needed with a long follow-up, in
14
15 particular for relatively rare cancer types. Meta-analyses have pooled the
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17 evidence of the gastrointestinal cancer preventive potential of aspirin and
18
19 other NSAIDs.[9-14] A large meta-analysis[15] and another detailed scientific
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21 assessment[16] concluded that a preventive effect on colorectal cancer was
22
23 especially pronounced in daily and long-term users (>5 years) in both
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25 interventional and observational studies.[15 16] Yet, the included studies used
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27 several different definitions of exposure, ranging from a single prescription of
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29 aspirin to daily use for >5 years, with too few studies reporting stratified
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31 analyses per dosage (or indication e.g. low dose anti-coagulants versus high
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33 dose analgesics) to draw reliable conclusions (although low dose has been
34
35 recommended by individual studies).[15] The statistical power was too low to
36
37 identify associations with many other types of (gastro-intestinal) cancer, and
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39 more, large original studies are needed to assess the potential preventive
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41 effect of other NSAIDs.[15]
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46 The role of PPI use on the association between NSAIDs with gastrointestinal
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48 cancer is insufficiently understood yet increasingly investigated, with growing
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50 evidence of carcinogenic and other long-term side-effects of PPIs.[17-20]
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3 The objective of this study was to assess the association of aspirin and other
4 NSAIDs on the risk of different gastrointestinal cancer types, while also
5 assessing the potential influence of concomitant PPI use.
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11 **Material and Methods**

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14 This nationwide Swedish population-based cohort study assessed the risk of
15 gastrointestinal cancer in adult NSAIDs users compared to the risk in the
16 entire Swedish background population of the corresponding sex, age and
17 calendar year (7.1-7.6 million adults). [21] [21] [21] [21] [21] [21] [21] [21] [21]
18 [21][21] Participants were enrolled during the study period from July 1, 2005
19 (the start of the Swedish Prescribed Drug Registry) to December 31, 2012.
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25 The cohort members were followed up until the occurrence of any cancer
26 (excluding non-melanoma skin cancer), death or December 31, 2012 (i.e. the
27 end of data collection for the Swedish Cancer Registry), whichever occurred
28 first. Individuals with a history of any cancer were excluded, as well as
29 individuals with a cancer diagnosis within 12 months after inclusion (to avoid
30 reverse causation). The unique 10-digit personal identity number, assigned to
31 each Swedish resident, was used for identification of all participants and for
32 linkages of their individual data between registries. This study was conducted
33 according to a detailed and a-priori established study protocol.
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49 **Data collection**

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51 The data for the present study were derived from our Chemoprevention of
52 cancer cohort. The study protocol conforms to the ethical guidelines of the
53 1975 Declaration of Helsinki as reflected in a prior approval by the institution's
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3 human research committee, the Regional Ethical Review Board in Stockholm,
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5 without need for informed consent (2014/1291-31/4, approved 27 AUG
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7 2014)(see Supplement 1 and [22-24]). This data collection originates from the
8
9 nationwide complete Swedish Prescribed Drug Registry, and includes all
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11 individuals residing in Sweden who have collected at least one dispensed
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13 prescription of any commonly prescribed drug between July 1, 2005 and
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15 December 31, 2014 (approximately 85% of all Swedish residents); with follow-
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17 up for cancer until December 31, 2012. This cohort has been linked to two
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19 other high-quality and complete nationwide Swedish registries, i.e. the
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21 Swedish Cancer Registry (>96% completeness of all cancers, originated in
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23 1961),[25] and the Swedish Causes of Death Registry (>99% completeness,
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25 originated in 1952), by means of the personal identity number.
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31 **Exposures**

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33 Therapy with systemic NSAIDs was defined as at least 6 months (≥ 180 days)
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35 cumulative exposure during the study period. This was a cumulative exposure
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37 based on the defined daily dosage (DDD) per prescribed package, which
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39 takes into account the potency of the drug as well as the prescribed quantity.
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41 Three main types of NSAIDs were categorized based on their mechanisms of
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43 action (selective or non-selective COX inhibition) and drug class (aspirin or
44
45 non-aspirin NSAIDs) with corresponding Anatomical Therapeutic Chemical
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47 classification codes (ATC): 1) aspirin (B01AC06, N02BA), 2) selective COX-2
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49 inhibitors (coxibs, M01AH), and 3) non-selective non-aspirin NSAIDs
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51 (remaining M01A codes). Individuals with ≥ 180 days of exposure to 2 or 3 of
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53 these groups were excluded, so the 3 groups are mutually exclusive. Users of
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3 combination preparations including aspirin, i.e. with corticosteroid (M01BA03),
4 PPIs (B01AC56), statins (C10BX), as well as preparations for local (oral) use
5 (A01AD05) were also excluded.
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9 Additionally, the relatively selective NSAIDs, a subgroup of the non-selective
10 NSAID users, containing meloxicam (M01AC06) and nabumetone
11 (M01AX01), were also analysed separately. Aspirin users were also divided in
12
13 2 groups according to their ATC code (≥ 180 days): low dose (B01AC06), and
14 high dose aspirin (N02BA) (those using both for ≥ 180 days were
15
16 excluded).[26] High-dose aspirin (N02BA) and some other NSAIDs
17
18 (Diclofenac, M01AB05 and Ibuprofen, M01AE01) are also available over the
19
20 counter in Sweden, but they are sold in only small packages and at higher
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22 prices per dose.[26 27] Thus, we can assume that maintenance users had
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24 their doses prescribed, and were thus recorded in the present study.
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33 **Outcomes**

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35 The outcome was a first gastrointestinal cancer diagnosis recorded in the
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37 Swedish Cancer Registry according to the International Classification of
38
39 Diseases (ICD) 10th edition. Gastrointestinal cancers were categorized as
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41 follows: any gastrointestinal cancer (C15-C26) or cancer of the oesophagus
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43 (C15), stomach (C16), small bowel (C17), colorectum (C18-C21), liver (C22),
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45 gallbladder or bile ducts (C23-24), or pancreas (C25). The category “other
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47 gastrointestinal cancer” (C26) was not analysed separately. Additionally, the
48
49 most common histological tumour types were analysed separately:
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51 adenocarcinoma (code 096) for oesophageal, gastric, gallbladder/biliary tract,
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53 pancreas and colorectal cancer; squamous cell carcinoma (code 146) for
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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

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

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

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38 Among all 1,368,027 users of NSAIDs, there were 783,870 (57.3%) aspirin
39 users, 566,209 (41.4%) non-selective NSAIDs users, and 17,948 (1.3%)
40 COX-2 users (Table 1, Supplement 1). Aspirin users were more likely to be
41 male (53.8%) and older than 70 years (54.9.2%), while non-selective NSAID
42 users and COX-2 users were predominantly female (62.8% and 59.9%,
43 respectively) and between 40 and 70 years of age (68.2% and 70.8%,
44 respectively). Use of PPIs was found in 25.6%, 26.2%, and 31.2% of the
45 aspirin users, non-selective NSAIDs users, and COX-2 users, respectively;
46 and use of statins in 55.2%, 13.7% and 14.4%, respectively. The majority of
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3 the population received their first prescription during the first half year of the
4 study period (2005), 54.9% of aspirin users, and 42.5% of non-selective
5 NSAIDs users (Supplement 2).
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10 **Aspirin**

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12 As presented in Table 1, 10,969 (1.40%) aspirin users developed some type
13 of gastrointestinal cancer during the follow-up. The most common cancer sites
14 were colorectal (n=6,919; 0.88%), gastric (n=1,079; 0.14%), and pancreatic
15 (n=1,114; 0.14%). There was no association with gastrointestinal cancer
16 based on the overall SIRs for aspirin users (SIR=1.02, 95% CI 1.00-1.04)
17 (Table 2). Shorter duration of use (<5.5 years) seemed to be associated with
18 an increased risk for all gastro-intestinal cancers. Yet, longer duration of
19 aspirin use was followed by a decreased SIR for gastrointestinal cancer
20 (SIR=0.31, 95% CI 0.30-0.33 for those with an estimated use between 5.5-7.7
21 years, and SIR=0.37, 95%CI 0.35-0.40 for >7.7 years) (Table 3) and long-
22 term aspirin users had clearly decreased SIRs for each gastrointestinal
23 cancer type (Table 3). The subgroup analyses including only the low-dosage
24 aspirin users (N=668,305, 85.3% of the aspirin cohort) showed lower SIRs for
25 all cancer locations, with significantly reduced risks for all locations except for
26 oesophageal, gastric and liver cancer (Table 4).
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48 **Non-selective NSAIDs**

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50 Table 1 shows that 3,428 (0.61%) of the non-selective NSAID users
51 developed cancer, mainly colorectal (n=2,017; 0.36%), pancreatic (n=490;
52 0.09%), and gastric cancers (n=260; 0.05%). Overall, there was a decreased
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3 risk of gastrointestinal cancer (SIR=0.79, 95%CI 0.77-0.82), and also for
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5 gastric (SIR=0.70, 95% CI 0.62-0.80), colorectal (SIR=0.74, 95% CI 0.71-
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7 0.77) and oesophageal (SIR=0.75, 95% CI 0.63-0.89) cancers analysed
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9 separately (and their main histological subtypes) (Table 2). There was no
10
11 evidence of decreased SIRs for the other types of gastrointestinal cancer
12
13 types, although the effect sizes indicated a decreased SIR of small bowel and
14
15 liver cancer. Longer duration of use of non-selective NSAIDs was associated
16
17 with a decreased gastrointestinal cancer risk for all anatomical locations
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19 (Table 3).
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24 ***Selective COX-2 inhibitors***

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

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44 Among the non-selective NSAIDs users, 7,609 individuals used relatively
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46 selective NSAIDs, of whom 74 (0.01%) developed cancer. There was no
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48 evidence for an association with any of the gastrointestinal cancer locations
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50 (Table 4).
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54 ***Aspirin with PPIs or statins***

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3 Users of aspirin with concomitant use of PPIs had higher SIRs for all
4 gastrointestinal cancers compared to those not using PPIs, with all SIRs
5 indicating an increased risk except for gallbladder cancer (Table 5). The SIRs
6 were especially increased for gastric cancer (SIR=1.89; 95% CI 1.73-2.06)
7 and oesophageal cancer (SIR=1.94; 95% CI 1.71-2.20). When using Poisson
8 regression to compare aspirin users using PPIs directly with aspirin users not
9 using PPIs (instead of using the background population as reference), the risk
10 was increased for all gastrointestinal cancers (IRR=1.19, 95% CI 1.11-1.26),
11 with significantly increased risks for oesophageal, gastric, small bowel, liver
12 and pancreatic cancer (Supplement 3).
13

14
15 Among aspirin users exposed to statins, the SIRs were close to unity for each
16 anatomical location (Table 5). When aspirin users using statins were directly
17 compared with aspirin users not using statins, risks were decreased for all
18 gastrointestinal cancers (IRR=0.81, 95% CI 0.77-0.85), with significant
19 decreases for all cancer locations except for colorectal and pancreatic cancer
20 (Supplement 3).
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42 ***Non-selective NSAIDs with PPIs or statins***

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44 In users of non-selective NSAIDs on therapy with PPIs, the SIRs were
45 increased for all gastrointestinal cancer types (and again higher than among
46 those not using PPIs), except for colorectal cancer (Table 5). When users of
47 non-selective NSAIDs using PPIs were directly compared with those not using
48 PPIs, risks were increased for all gastrointestinal cancers (IRR=1.61, 95% CI
49 1.49-1.74), and each individual cancer location except for gallbladder cancer
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3 (Supplement 3). Among non-selective NSAIDs users using statins, the SIRs
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5 were lower than among all users of non-selective NSAIDs, and significantly
6
7 reduced for oesophageal, gastric and colorectal cancer. When users of non-
8
9 selective NSAIDs using statins were directly compared with those not using
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11 statins, risks were decreased for all gastrointestinal cancers (IRR=0.86, 95%
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13 CI 0.76-0.96), yet not significant for the individual cancer locations
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16 (Supplement 3).
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20 **Discussion**

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22 This study on contemporary use of NSAIDs showed a decreased risk of all
23
24 types of gastrointestinal cancer among long-term users of aspirin (>5.5 years)
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26 and non-selective NSAIDs users even for shorter duration of use (>0.7 years).
27
28 Long-term users of non-selective NSAIDs were at a particularly decreased
29
30 risk for gastric, oesophageal, and colorectal cancers. These seemingly
31
32 protective associations might be counteracted by concomitant PPI therapy,
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34 and enhanced by concomitant statin use.
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41 The main strengths of this study are the population-based design and large
42
43 sample size, including all adults residing in Sweden during the study period,
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45 which enabled separate analyses for contemporary use of different types of
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47 NSAIDs, and evaluation of less common types of gastrointestinal cancer
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49 which could not be assessed previously because of insufficient power, in
50
51 particular for non-aspirin NSAIDs. Other advantages include the complete
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53 follow-up and accurate censoring for mortality. The data on the exposures
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55 (medications) and outcomes (gastrointestinal cancers) were highly accurate
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3 due to the validity and completeness of the Swedish registries, eliminating
4 recall bias.
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9 Although our findings for aspirin are largely consistent with the literature, that
10 the protective effect is only seen after 5 years, reverse causation, confounding
11 and/or bias appear to influence the aspirin analyses because of the apparent
12 initial increased risk of cancer among short-term users. By excluding all
13 individuals diagnosed with cancer within a year after enrolment, and only
14 including those with a minimal accumulated duration of use of 6 months, the
15 risk of reverse causation should be reduced. Yet, our results indicate that
16 those with an estimated duration shorter than 5 years have an apparent
17 increased risk, which might be because they take aspirin because of cancer-
18 related pain or thrombotic events – indicating confounding by indication and
19 reverse causation among the group with the shortest exposure time, an effect
20 which could not have been detected in intervention trials or in case-control
21 studies with a study-design-inherent more restrictive selection of study
22 participants.[15 29] As previous studies reported, 15-20% of cancer patients
23 have thrombotic complications during the course of the disease (often as early
24 manifestation of an occult malignancy),[30] yet these complications (e.g. deep
25 venous thrombosis) are more likely to be treated with anti-coagulants than
26 aspirin. However, when only looking at those exclusively using low-dose
27 aspirin for ≥ 180 days, i.e. the platelet aggregation inhibitors, the protective
28 effects were also visible in the overall analyses non taking into account
29 duration, with SIR=0.86 (95%CI 0.85-0.88). This indicates that the apparent
30 increased risks are mainly because of the small group using aspirin as
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3 analgesic (high dose), which shows it is important to distinguish between both
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5 groups of aspirin-use. Reverse causality seems to be less of a problem for
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7 other NSAIDs users, although these may be used as analgesics.[31] Yet,
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9 individuals using NSAIDs may be at a lower a-priori risk of developing gastro-
10
11 intestinal cancer, because individuals with upper gastro-intestinal symptoms
12
13 are less likely to be chronic NSAIDs users due to the risk of gastro-intestinal
14
15 side-effects.

16
17 Especially for aspirin users (with a high cardiovascular mortality), death is a
18
19 competing risk for the development of cancer, reducing the number at risk to
20
21 develop cancer. Therefore, we censored follow-up time at time of death. In
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23 this cohort the standardised mortality risks were 9.64 (95%CI 9.60-9.69) for
24
25 aspirin users and 2.08 (95% CI 2.05-2.11) for non-selective non-aspirin
26
27 NSAIDs users indeed showing a higher risk of death competing with the risk
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29 of cancer.
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35 Another limitation is potential confounding, e.g. by socio-economic status,
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37 dietary factors, obesity, tobacco smoking, and alcohol consumption, which
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39 could not be taken into account since such information was not available for
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41 the total background population. However, we adjusted for age, sex and
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43 calendar period. We may have incomplete exposure ascertainment (and
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45 underestimation of duration of use) for part of our cohort since no information
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47 was available on prescriptions before July 2005 or over-the-counter use. Yet,
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49 potential long-term (protective) effects may be expected to decrease gradually
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51 yet significantly after treatment cessation, reducing the potential effect of
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53 misclassification on our results due to exposure before 2005. We used the
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3 minimal exposure criterion of 180 days to exclude occasional users who are
4 more likely to obtain their NSAIDs over-the-counter, so at a higher price. We
5 did not have data on used daily dosage or duration of use, and used a proxy
6 variable for duration based on accumulation of the average DDDs per
7 package. This explains why some aspirin users had an estimated exposure
8 time longer than the duration of follow-up, indicating a high daily dose. The
9 high variability in actual and estimated administered dosage also hindered
10 assessment of recency of use. Some previous studies subdivided aspirin use
11 into “low dose” and “high dose” based on prescribed dosages (e.g. <75
12 mg/day[32] or <100 mg/day[14]), but since we did not have information on the
13 number of prescribed pills per day, and different dosages could have been
14 prescribed during the study period, we used the definition based on ATC
15 coding and assessed the estimated duration of use, with the additional
16 advantage that the low-dose aspirin was only available on prescription. This
17 should also be a more accurate reflection of duration of use than the number
18 of prescriptions.[9] In our study, the DDD per package could range from <5 to
19 500 (for other NSAIDs) or 1000 (for aspirin), which illustrates the variation
20 between prescriptions. Since 1.4 million individuals were exposed to NSAIDs
21 (≥ 180 days), i.e. one fifth of the adult population in Sweden, our results are
22 likely to be diluted since we compared them with the total background
23 population. Yet, despite this dilution the associations among long-term users
24 were strongly decreased.

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52 Compared to previous studies, this study was better powered to separately
53 analyses different gastrointestinal cancers and types of NSAIDs.[33] The
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3 above mentioned meta-analysis[15] identified only 2 cohort studies including
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5 over 100,000 individuals assessing colorectal cancer risk among aspirin-
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7 users.[34 35] Even our exposed groups for aspirin and non-selective NSAIDs
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9 alone were 5-7 times larger than earlier large studies. The decrease in
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11 gastrointestinal cancer risk became evident only after longer exposure, which
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13 has also been shown in previous research,[15 36] and is biologically plausible
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15 given the expected time latency for (hindering) cancer progression.
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20 The higher risk among aspirin and other NSAID users also using PPIs should
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22 be interpreted with some caution. PPIs are often prescribed for
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24 gastroesophageal reflux and peptic ulcers, which are risk factors for
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26 oesophageal and gastric cancer, respectively. Therefore, a higher cancer risk
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28 was expected for those locations, yet not for the other gastrointestinal cancer
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30 types. PPIs can also be used to prevent peptic ulcers in users of aspirin and
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32 other NSAIDs, usually in individuals without any gastro-intestinal morbidity.
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35 Another study of our group based on the same source cohort,[24] investigated
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37 the risk of gastric cancer among PPI maintenance users, which suggested an
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39 increased risk in all indication groups for PPI (including those without
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41 gastrointestinal symptoms); which also supports a potential independent role
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43 for PPI in carcinogenesis as also suggested recently by other groups.[37 38]
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45 Together with a potential increased risk of mortality related to long-term PPI
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47 use,[39] we believe a more careful approach should be considered when
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49 prescribing PPIs to prevent gastrointestinal complications in long-term
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51 NSAIDs users. Yet, the risk for gastrointestinal complications such as
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53 bleeding should be assessed on an individual bases based on other research
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3 investigating shorter-term effects.[40] Before considering implementing aspirin
4 or other NSAIDs as wide-spread intervention, safety, in particular considering
5 long-term use, needs to be considered, with previous research tending
6 towards a “favourable benefit harm-profile” despite an excess risk of
7 bleeding.[41]
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15 To conclude, this large Swedish nationwide and population-based cohort
16 study on contemporary and long-term use of NSAIDs indicates a strongly
17 protective effect of long-term use of both (low-dose) aspirin and other non-
18 selective NSAIDs on gastrointestinal cancer development.
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37 the data and the accuracy of the data analysis. NB conducted and is
38 responsible for the data-analysis. Literature search: NB; Design of the study:
39 both authors; Data collection and preparation for analyses: NB; Data analysis:
40 NB; Data interpretation: both authors; Writing of first draft: NB, revised and
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8
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13 **Competing interests:** none
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16 **Data sharing statement:** We are willing to share data upon request after
17
18 ethics approval has been approved by the relevant committee and the
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20 governmental agencies that maintain the data.
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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
	<i>Number (%)</i>	<i>Number (%)</i>	<i>Number (%)</i>
Total	783,870	566,209	17,948
Sex			
<i>Men</i>	421,609 (53.8)	210,705 (37.2)	7,201 (40.1)
<i>Women</i>	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)			
<i>yes</i>	200,828 (25.6)	148,586 (26.2)	5,602 (31.2)
<i>no</i>	583,042 (74.4)	417,623 (73.8)	12,346 (68.8)
Statins use (≥180 days)			
<i>yes</i>	432,996 (55.2)	77,514 (13.7)	2,589 (14.4)
<i>no</i>	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)
<i>Adenocarcinoma</i>	319 (0.04)	75 (0.01)	4 (0.02)
<i>Squamous cell carcinoma</i>	203 (0.03)	50 (0.01)	2 (0.01)
Gastric cancer	1,079 (0.14)	260 (0.05)	7 (0.04)
<i>Adenocarcinoma</i>	949 (0.12)	212 (0.04)	3 (0.02)
Small bowel cancer	253 (0.03)	94 (0.02)	5 (0.03)
<i>Carcinoid</i>	122 (0.02)	43 (0.01)	2 (0.01)
Colorectal cancer	6,919 (0.88)	2,017 (0.36)	60 (0.33)
<i>Adenocarcinoma</i>	6,608 (0.84)	1,887 (0.33)	59 (0.33)
Liver cancer	645 (0.08)	232 (0.04)	3 (0.02)
<i>Hepatocellular carcinoma</i>	358 (0.05)	100 (0.02)	1 (0.01)
Gallbladder and biliary tract cancer	385 (0.05)	190 (0.03)	5 (0.03)
<i>Adenocarcinoma</i>	288 (0.04)	149 (0.03)	2 (0.01)
Pancreatic cancer	1,114 (0.14)	490 (0.09)	13 (0.07)
<i>Adenocarcinoma</i>	835 (0.11)	402 (0.07)	11 (0.06)

1	Other gastrointestinal cancer	35 (0.00)	11 (0.00)	0 (0.00)
2	<hr/>			
3	Duration of follow-up in person-years			
4	<i>Total</i>	3,776,237	3,376,275	82,733
5	<i>Mean (standard deviation)</i>	4.82 (2.40)	5.96 (1.67)	4.61 (2.21)
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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)
<i>Men</i>	6,659	1.24 (1.21-1.27)	1,390	0.78 (0.74-0.82)
<i>Women</i>	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)
<i>Adenocarcinoma</i>	319	1.17 (1.04-1.30)	75	0.81 (0.64-1.01)
<i>Squamous cell carcinoma</i>	203	1.06 (0.92-1.22)	50	0.66 (0.49-0.87)
<i>Men</i>	415	1.09 (0.99-1.20)	90	0.88 (0.63-0.97)
<i>Women</i>	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)
<i>Adenocarcinoma</i>	949	1.07 (1.00-1.14)	212	0.66 (0.58-0.76)
<i>Men</i>	714	1.08 (1.00-1.16)	128	0.72 (0.60-0.85)
<i>Women</i>	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)
<i>Carcinoid</i>	122	1.11 (0.92-1.32)	43	0.84 (0.61-1.13)
<i>Men</i>	150	1.05 (0.89-1.23)	34	0.72 (0.50-1.00)
<i>Women</i>	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)
	<i>Adenocarcinoma</i>	6,608	1.00 (0.80-1.03)	1,887	0.74 (0.70-0.77)
	<i>Men</i>	4,105	1.03 (1.00-1.06)	793	0.73 (0.68-0.79)
	<i>Women</i>	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)
	<i>Hepatocellular carcinoma</i>	358	1.13 (1.02-1.25)	100	0.83 (0.77-1.01)
	<i>Men</i>	449	1.12 (1.02-1.23)	130	1.00 (0.84-1.19)
	<i>Women</i>	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)
	<i>Adenocarcinoma</i>	288	0.93 (0.82-1.04)	149	1.07 (0.90-1.25)
	<i>Men</i>	181	1.00 (0.86-1.15)	50	0.98 (0.73-1.29)
	<i>Women</i>	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)
	<i>Adenocarcinoma</i>	835	1.00 (0.93-1.07)	402	1.02 (0.92-1.13)
	<i>Men</i>	629	1.07 (0.99-1.16)	163	0.89 (0.76-1.03)
	<i>Women</i>	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)

	<i>5.5-7.7 years</i>	813	0.31 (0.29-0.33)	<i>1.1-2.1 years</i>	565	0.78 (0.72-0.85)
	<i>>7.7 years</i>	604	0.36 (0.33-0.39)	<i>>2.1 years</i>	423	0.47 (0.43-0.52)
Liver cancer						
	<i>0.5-2.5 years</i>	222	2.63 (2.30-3.00)	<i>0.5-0.7 years</i>	63	1.23 (0.95-1.57)
	<i>2.5-5.5 years</i>	272	1.96 (1.74-2.21)	<i>0.7-1.1 years</i>	53	1.02 (0.76-1.33)
	<i>5.5-7.7 years</i>	100	0.44 (0.35-0.53)	<i>1.1-2.1 years</i>	70	1.10 (0.86-1.39)
	<i>>7.7 years</i>	51	0.40 (0.30-0.53)	<i>>2.1 years</i>	46	0.61 (0.45-0.81)
Gallbladder and biliary tract cancer						
	<i>0.5-2.5 years</i>	137	2.36 (1.98-2.79)	<i>0.5-0.7 years</i>	42	1.17 (0.85-1.58)
	<i>2.5-5.5 years</i>	143	1.52 (1.28-1.79)	<i>0.7-1.1 years</i>	51	1.34 (1.00-1.76)
	<i>5.5-7.7 years</i>	61	0.39 (0.30-.50)	<i>1.1-2.1 years</i>	52	1.06 (0.79-1.39)
	<i>>7.7 years</i>	44	0.40 (0.29-0.53)	<i>>2.1 years</i>	45	0.73 (0.53-0.98)
Pancreatic cancer						
	<i>0.5-2.5 years</i>	424	2.79 (2.53-3.06)	<i>0.5-0.7 years</i>	107	1.09 (0.90-1.32)
	<i>2.5-5.5 years</i>	467	1.87 (1.71-2.06)	<i>0.7-1.1 years</i>	123	1.20 (1.00-1.43)
	<i>5.5-7.7 years</i>	149	0.36 (0.30-0.42)	<i>1.1-2.1 years</i>	136	1.05 (0.88-1.25)
	<i>>7.7 years</i>	74	0.28 (0.23-0.37)	<i>>2.1 years</i>	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		Relatively selective NSAIDs		Low-dose aspirin (n=668,305)	
	maintenance users (n=17,948)		maintenance users (n=7,609)		Number	
	<i>Number</i>		<i>Number of</i>		<i>Number</i>	
	<i>of cases</i>	<i>SIRS (95% CI)</i>	<i>cases</i>	<i>SIRS (95% CI)</i>	<i>of cases</i>	<i>SIRS (95% CI)</i>
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)	
	<i>Number of cases</i>	<i>SIRs (95% CI)</i>	<i>Number of cases</i>	<i>SIRs (95% CI)</i>	<i>Number of cases</i>	<i>SIRs (95% CI)</i>
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)	
	<i>Number of cases</i>	<i>SIRs (95% CI)</i>	<i>Number of cases</i>	<i>SIRs (95% CI)</i>	<i>Number of cases</i>	<i>SIRs (95% CI)</i>
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)

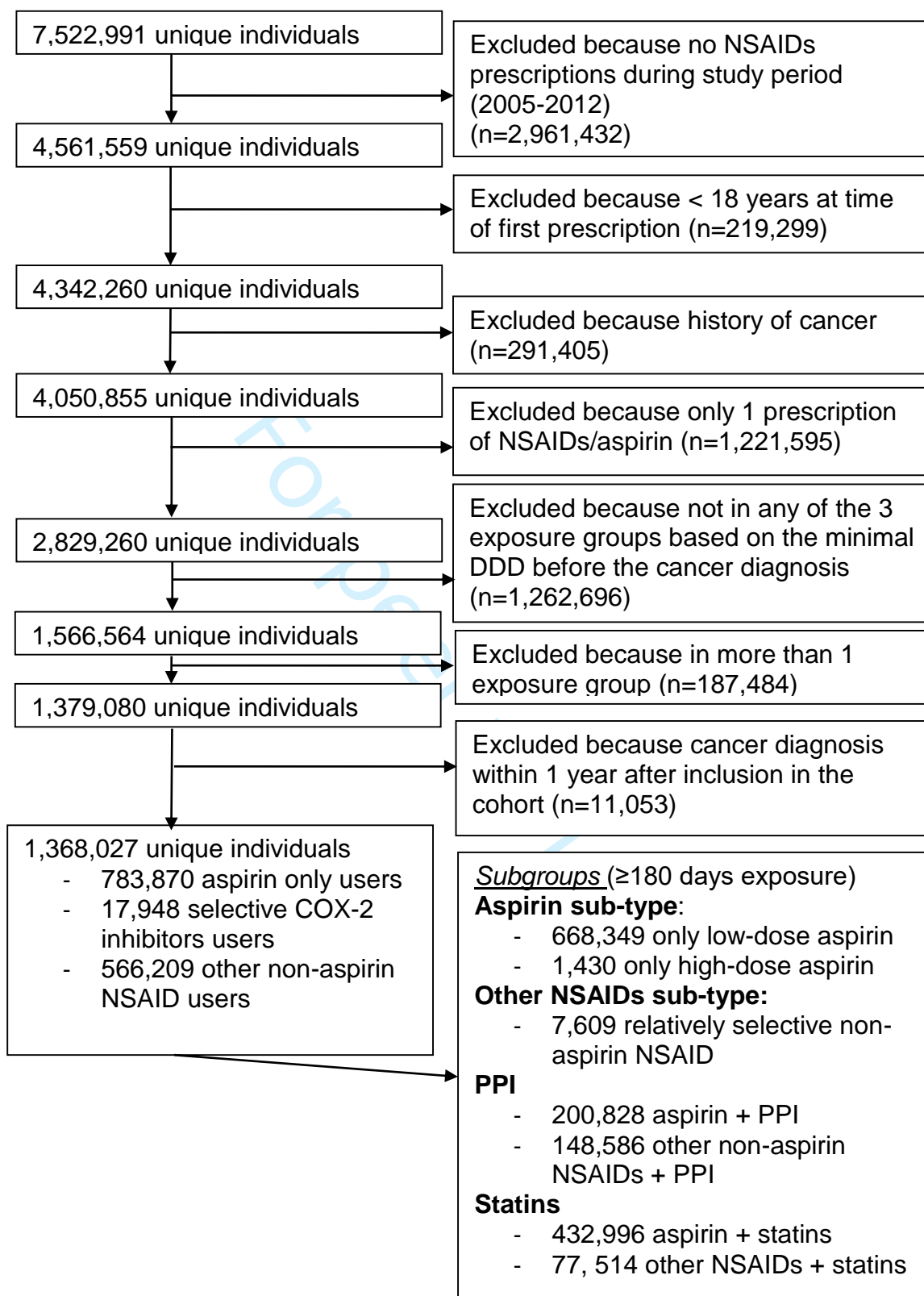
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Online Supplement 1

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

For peer review only

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

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2 This cohort included all individuals residing in Sweden who received at least one
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4 dispensed prescription of one of the following commonly prescribed drugs between July 1,
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6 2005 and December 31, 2014 (with corresponding ATC codes) with follow-up for cancer
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8 until December 2012: sex hormones (G03), drugs for peptic ulcers and gastro-esophageal
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10 reflux disease (A02B), acetylsalicylic acid (B01AC06, N02BA), non-steroidal anti-
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12 inflammatory drugs (M01A), HMG CoA reductase inhibitors (C10AA), drugs affecting bone
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14 structure and mineralization, (M05B), and antibiotics (J01AA, J01CA04, J01FA, J01MA,
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16 J01XD, J01XE, J04AB04). This cohort included approximately 85% of all Swedish
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18 residents, with especially high coverage of adults.
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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
	<i>N (%)</i>	<i>N (%)</i>
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).

	Non-selective			
	Aspirin with PPI vs. without	Aspirin with statin vs. without	non-aspirin NSAIDs with PPI vs. without	Non-selective non-aspirin NSAIDs with statins vs. without
	<i>IRR (95% CI)</i>	<i>IRR (95% CI)</i>	<i>IRR (95% CI)</i>	<i>IRR (95% CI)</i>
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

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Manuscript ID	bmjopen-2018-021869.R1
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3 **Maintenance use of non-steroidal anti-inflammatory drugs**
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5 **and risk of gastrointestinal cancer in a nationwide population-**
6 **based cohort study in Sweden.**
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10 **Running title: NSAIDs and gastrointestinal cancer prevention**

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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

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3 were using PPIs, had higher risks for all gastrointestinal cancer types; and
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5 lower risk if using statins.
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7 **Conclusion:** Long-term use of (low-dose) aspirin and non-selective NSAIDs
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9 was associated with a decreased risk of all gastrointestinal cancer types.
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13 **Key words:** gastro-intestinal cancer, chemoprevention, non-steroidal anti-
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15 inflammatory drugs, aspirin, coxibs, cancer, pharmaco-epidemiology.
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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

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3 of cardiovascular morbidity for COX-2 selective inhibitors compared to
4 nonselective COX-inhibitors.[3 7 8] Some of the older NSAIDs are “relatively
5 selective COX-2 inhibitors”, i.e. nabumetone, meloxicam, etodolac and
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7 nimesulide.[3]
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11 However, epidemiological evidence to support a chemopreventive effect is still
12 limited, mainly because large numbers are needed with a long follow-up, in
13 particular for relatively rare cancer types. Meta-analyses have pooled the
14 evidence of the gastrointestinal cancer preventive potential of aspirin and
15 other NSAIDs.[9-14] A large meta-analysis[15] and another detailed scientific
16 assessment[16] concluded that a preventive effect on colorectal cancer was
17 especially pronounced in daily and long-term users (>5 years) in both
18 interventional and observational studies,[15 16] with similar findings in recent
19 studies on gastric cancer.[17 18] Yet, these studies used several different
20 definitions of exposure, ranging from a single prescription of aspirin to daily
21 use for >5 years, with too few studies reporting stratified analyses per dosage
22 (or indication e.g. low dose anti-coagulants versus high dose analgesics) to
23 draw reliable conclusions (although low dose has been recommended by
24 individual studies).[15] The statistical power was too low to identify
25 associations with many other types of (gastro-intestinal) cancer, and more,
26 large original studies are needed to assess the potential preventive effect of
27 other NSAIDs.[15]
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31 The role of PPI use on the association between NSAIDs with gastrointestinal
32 cancer is insufficiently understood yet increasingly investigated, with growing
33 evidence of carcinogenic and other long-term side-effects of PPIs.[19-22]
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3 The objective of this study was to assess the association of aspirin and other
4 NSAIDs on the risk of different gastrointestinal cancer types, while also
5 assessing the potential influence of concomitant PPI use.
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10 11 **Material and Methods**

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

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51 The data for the present study were derived from our Chemoprevention of
52 cancer cohort. The study protocol conforms to the ethical guidelines of the
53 1975 Declaration of Helsinki as reflected in a prior approval by the institution's
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3 human research committee, the Regional Ethical Review Board in Stockholm,
4 without need for informed consent (2014/1291-31/4, approved 27 AUG
5 2014)(see Supplement 1 and [24-26]). This data collection originates from the
6 nationwide complete Swedish Prescribed Drug Registry, and includes all
7 individuals residing in Sweden who have collected at least one dispensed
8 prescription of any commonly prescribed drug between July 1, 2005 and
9 December 31, 2014 (approximately 85% of all Swedish residents); with follow-
10 up for cancer until December 31, 2012. This cohort has been linked to two
11 other high-quality and complete nationwide Swedish registries, i.e. the
12 Swedish Cancer Registry (>96% completeness of all cancers, originated in
13 1961),[27] and the Swedish Causes of Death Registry (>99% completeness,
14 originated in 1952), by means of the personal identity number.
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31 **Exposures**

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33 Therapy with systemic NSAIDs was defined as at least 6 months (≥ 180 days)
34 cumulative exposure during the study period. This was a cumulative exposure
35 based on the defined daily dosage (DDD) per prescribed package, which
36 takes into account the potency of the drug as well as the prescribed quantity.
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38 Three main types of NSAIDs were categorized based on their mechanisms of
39 action (selective or non-selective COX inhibition) and drug class (aspirin or
40 non-aspirin NSAIDs) with corresponding Anatomical Therapeutic Chemical
41 classification codes (ATC): 1) aspirin (B01AC06, N02BA), 2) selective COX-2
42 inhibitors (coxibs, M01AH), and 3) non-selective non-aspirin NSAIDs
43 (remaining M01A codes). Individuals with ≥ 180 days of exposure to 2 or 3 of
44 these groups were excluded, so the 3 groups are mutually exclusive. Users of
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3 combination preparations including aspirin, i.e. with corticosteroid (M01BA03),
4 PPIs (B01AC56), statins (C10BX), as well as preparations for local (oral) use
5 (A01AD05) were also excluded.
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9 Additionally, the relatively selective COX-2 inhibitors, a subgroup of the non-
10 selective NSAID users, containing meloxicam (M01AC06) and nabumetone
11 (M01AX01), were also analysed separately. Aspirin users were also divided in
12 2 groups according to their ATC code (≥ 180 days): low dose (B01AC06), and
13 high dose aspirin (N02BA) (those using both for ≥ 180 days were
14 excluded).[28] High-dose aspirin (N02BA) and some other NSAIDs
15 (Diclofenac, M01AB05 and Ibuprofen, M01AE01) are also available over the
16 counter in Sweden, but they are sold in only small packages and at higher
17 prices per dose.[28 29] Thus, we can assume that maintenance users had
18 their doses prescribed, and were thus recorded in the present study.
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33 **Outcomes**

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35 The outcome was a first gastrointestinal cancer diagnosis recorded in the
36 Swedish Cancer Registry according to the International Classification of
37 Diseases (ICD) 10th edition, including all cancers of the alimentary and
38 hepatobiliary tract. Gastrointestinal cancers were categorized as follows: any
39 gastrointestinal cancer (C15-C26) or cancer of the oesophagus (C15),
40 stomach (C16), small bowel (C17), colorectum (C18-C21), liver, including
41 intrahepatic bile ducts (C22), gallbladder or extrahepatic bile ducts (C23-24),
42 or pancreas (C25). The category "other gastrointestinal cancer" (C26) was not
43 analysed separately. Additionally, the most common histological tumour types
44 were analysed separately: adenocarcinoma (code 096) for oesophageal,
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3 gastric, gallbladder/biliary tract, pancreas and colorectal cancer; squamous
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5 cell carcinoma (code 146) for oesophageal cancer; hepatocellular carcinoma
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7 (code 066) and cholangiocarcinoma (code 076) for liver cancer; and carcinoid
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9 (code 086) for small bowel cancer.
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11 12 13 14 **Statistical analyses**

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17 The relative risks of developing gastrointestinal cancer in individuals exposed
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19 to the drugs under study were standardized using the Swedish background
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21 population of the corresponding age, sex, and calendar period. Standardized
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23 incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated,
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25 while accounting for changes in age and calendar categories when calculating
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27 years of follow-up.[30] Follow-up time was counted from the dispense date of
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29 the first NSAID prescription to the date of a first cancer diagnosis, death, or
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31 the end of the study (31st December 2012), whichever occurred first. The
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33 expected incidence rates were calculated from cancer data recorded in the
34
35 Swedish Cancer Registry and the age-stratified number of individuals per
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37 calendar year according to Statistics Sweden (Population Statistics). The
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39 overall SIR for gastrointestinal cancer was calculated, as well as SIRs for
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41 each anatomical location separately, including sub-analyses for the most
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43 common histological types. The analyses were also stratified for sex and age
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45 for each cancer type. Subgroup analyses were performed for high-dose and
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47 low-dose aspirin, users of relatively selective COX-2 inhibitors, NSAID use
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49 with concurrent PPI (A02BC) or statin (C10AA) use (≥ 180 days) if the groups
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51 were sufficiently large. To assess the effect of PPI and statins, a multivariable
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53 Poisson regression model was fitted, adjusting for age at first prescription, sex
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3 and interaction between PPI and statins, and presented as incidence rate
4 ratios (IRR) and 95%CI. The duration of the exposures was assessed by
5 dividing the total cumulative dosage (sum of DDDs per package) received
6 before the cancer diagnosis into four equally sized groups (quartiles), yet their
7 total follow-up time was taken into account for the analyses. There were no
8 missing data on exposures, outcomes or confounding variables. Effect
9 estimates were only reported when at least 5 individuals developed the
10 outcome.
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22 ***Patient involvement***

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

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42 Among all 1,368,027 users of NSAIDs, there were 783,870 (57.3%) aspirin
43 users, 566,209 (41.4%) non-selective NSAIDs users, and 17,948 (1.3%)
44 COX-2 users (Table 1, Supplement 1). Aspirin users were more likely to be
45 male (53.8%) and older than 70 years (54.9.2%), while non-selective NSAID
46 users and COX-2 users were predominantly female (62.8% and 59.9%,
47 respectively) and between 40 and 70 years of age (68.2% and 70.8%,
48 respectively). Use of PPIs was found in 25.6%, 26.2%, and 31.2% of the
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3 aspirin users, non-selective NSAIDs users, and COX-2 users, respectively;
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5 and use of statins in 55.2%, 13.7% and 14.4%, respectively. The majority of
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7 the population received their first prescription during the first half year of the
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9 study period (2005), 54.9% of aspirin users, and 42.5% of non-selective
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11 NSAIDs users (Supplement 2).
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14 15 **Aspirin**

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17 As presented in Table 1, 10.969 (1.40%) aspirin users developed some type
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19 of gastrointestinal cancer during the follow-up. The most common cancer sites
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21 were colorectal (n=6,919; 0.88%), gastric (n=1,079; 0.14%), and pancreatic
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23 (n=1,114; 0.14%). There was no association with gastrointestinal cancer
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25 based on the overall SIRs for aspirin users (SIR=1.02, 95% CI 1.00-1.04)
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27 (Table 2). Shorter duration of use (<5.5 years) seemed to be associated with
28
29 an increased risk for all gastro-intestinal cancers. Yet, longer duration of
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31 aspirin use was followed by a decreased SIR for gastrointestinal cancer
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33 (SIR=0.31, 95% CI 0.30-0.33 for those with an estimated use between 5.5-7.7
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35 years, and SIR=0.37, 95%CI 0.35-0.40 for >7.7 years) (Table 3) and long-
36
37 term aspirin users had clearly decreased SIRs for each gastrointestinal
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39 cancer type (Table 3). The subgroup analyses including only the low-dosage
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41 aspirin users (N=668,305, 85.3% of the aspirin cohort) showed lower SIRs for
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43 all cancer locations, with significantly reduced risks for all locations except for
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45 oesophageal, gastric and liver cancer (Supplement 3).
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52 **Non-selective NSAIDs**

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3 Table 1 shows that 3,428 (0.61%) of the non-selective NSAID users
4 developed cancer, mainly colorectal (n=2,017; 0.36%), pancreatic (n=490;
5 0.09%), and gastric cancers (n=260; 0.05%). Overall, there was a decreased
6 risk of gastrointestinal cancer (SIR=0.79, 95%CI 0.77-0.82), and also for
7 gastric (SIR=0.70, 95% CI 0.62-0.80), colorectal (SIR=0.74, 95% CI 0.71-
8 0.77) and oesophageal (SIR=0.75, 95% CI 0.63-0.89) cancers analysed
9 separately (and their main histological subtypes) (Table 2). There was no
10 evidence of decreased SIRs for the other types of gastrointestinal cancer
11 types, although the effect sizes indicated a decreased SIR of small bowel and
12 liver cancer. Longer duration of use of non-selective NSAIDs was associated
13 with a decreased gastrointestinal cancer risk for all anatomical locations
14 (Table 3).
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31 ***Selective COX-2 inhibitors***

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

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50 Among the non-selective NSAIDs users, 7,609 individuals used relatively
51 selective COX-2 inhibitors, of whom 74 (0.01%) developed cancer. There was
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3 no evidence for an association with any of the gastrointestinal cancer
4 locations (Supplement 3).
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8 9 ***Aspirin with PPIs or statins***

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11 Users of aspirin with concomitant use of PPIs had higher SIRs for all
12 gastrointestinal cancers compared to those not using PPIs, with all SIRs
13 indicating an increased risk except for gallbladder cancer (Table 4). The SIRs
14 were especially increased for gastric cancer (SIR=1.89; 95% CI 1.73-2.06)
15 and oesophageal cancer (SIR=1.94; 95% CI 1.71-2.20). When using Poisson
16 regression to compare aspirin users using PPIs directly with aspirin users not
17 using PPIs (instead of using the background population as reference), the risk
18 was increased for all gastrointestinal cancers (IRR=1.19, 95% CI 1.11-1.26),
19 with significantly increased risks for oesophageal, gastric, small bowel, liver
20 and pancreatic cancer (Supplement 4).
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33 Among aspirin users exposed to statins, the SIRs were close to unity for each
34 anatomical location (Table 4). When aspirin users using statins were directly
35 compared with aspirin users not using statins, risks were decreased for all
36 gastrointestinal cancers (IRR=0.81, 95% CI 0.77-0.85), with significant
37 decreases for all cancer locations except for colorectal and pancreatic cancer
38 (Supplement 4).
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50 51 ***Non-selective NSAIDs with PPIs or statins***

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53 In users of non-selective NSAIDs on therapy with PPIs, the SIRs were
54 increased for all gastrointestinal cancer types (and again higher than among
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3 those not using PPIs), except for colorectal cancer (Table 4). When users of
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5 non-selective NSAIDs using PPIs were directly compared with those not using
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7 PPIs, risks were increased for all gastrointestinal cancers (IRR=1.61, 95% CI
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9 1.49-1.74), and each individual cancer location except for gallbladder cancer
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11 (Supplement 4). Among non-selective NSAIDs users using statins, the SIRs
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13 were lower than among all users of non-selective NSAIDs, and significantly
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15 reduced for oesophageal, gastric and colorectal cancer. When users of non-
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17 selective NSAIDs using statins were directly compared with those not using
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19 statins, risks were decreased for all gastrointestinal cancers (IRR=0.86, 95%
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21 CI 0.76-0.96), yet not significant for the individual cancer locations
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23 (Supplement 4).
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29 Discussion

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31 This study on contemporary use of NSAIDs showed a decreased risk of all
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33 types of gastrointestinal cancer among long-term users of aspirin (>5.5 years)
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35 and non-selective NSAIDs users even for shorter duration of use (>0.7 years).
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37 Long-term users of non-selective NSAIDs were at a particularly decreased
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39 risk for gastric, oesophageal, and colorectal cancers. These seemingly
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41 protective associations might be counteracted by concomitant PPI therapy,
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43 and enhanced by concomitant statin use.
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49 The main strengths of this study are the population-based design and large
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51 sample size, including all adults residing in Sweden during the study period,
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53 which enabled separate analyses for contemporary use of different types of
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55 NSAIDs, and evaluation of less common types of gastrointestinal cancer
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3 which could not be assessed previously because of insufficient power, in
4 particular for non-aspirin NSAIDs. Other advantages include the complete
5 follow-up and accurate censoring for mortality. The data on the exposures
6 (medications) and outcomes (gastrointestinal cancers) were highly accurate
7 due to the validity and completeness of the Swedish registries, eliminating
8 recall bias.
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18 Although our findings for aspirin are largely consistent with the literature, that
19 the protective effect is only seen after 5 years, reverse causation, confounding
20 and/or bias appear to influence the aspirin analyses because of the apparent
21 initial increased risk of cancer among short-term users. By excluding all
22 individuals diagnosed with cancer within a year after enrolment, and only
23 including those with a minimal accumulated duration of use of 6 months, the
24 risk of reverse causation should be reduced. Yet, our results indicate that
25 those with an estimated duration shorter than 5 years have an apparent
26 increased risk, which might be because they take aspirin because of yet
27 undiagnosed cancer-related pain or thrombotic events – indicating
28 confounding by indication and reverse causation among the group with the
29 shortest exposure time, an effect which could not have been detected in
30 intervention trials or in case-control studies with a study-design-inherent more
31 restrictive selection of study participants.[15 31] As previous studies reported,
32 15-20% of cancer patients have thrombotic complications during the course of
33 the disease (often as early manifestation of an occult malignancy),[32] yet
34 these complications (e.g. deep venous thrombosis) are more likely to be
35 treated with anti-coagulants than aspirin. However, when only looking at those
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3 exclusively using low-dose aspirin for ≥ 180 days, i.e. the platelet aggregation
4 inhibitors, the protective effects were also visible in the overall analyses non
5 taking into account duration, with SIR=0.86 (95%CI 0.85-0.88). This indicates
6 that the apparent increased risks are mainly because of the small group using
7 aspirin as analgesic (high dose), which shows it is important to distinguish
8 between both groups of aspirin-use. Reverse causality seems to be less of a
9 problem for other NSAIDs users, although these may be used as
10 analgesics.[33] Yet, individuals using NSAIDs may be at a lower a-priori risk
11 of developing gastro-intestinal cancer, because individuals with upper gastro-
12 intestinal symptoms are less likely to be chronic NSAIDs users due to the risk
13 of gastro-intestinal side-effects.

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

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48 Another limitation is potential confounding, e.g. by socio-economic status,
49 dietary factors, obesity, tobacco smoking, and alcohol consumption, which
50 could not be taken into account since such information was not available for
51 the total background population. However, we adjusted for age, sex and
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3 calendar period. Cancer-type specific confounders and their treatment such
4 as *Helicobacter pylori* for gastric cancer, hepatitis B/C infection for liver cancer
5 and chronic inflammatory diseases such as inflammatory bowel disease for
6 bowel cancer and pancreatitis for pancreatic cancer, may also have
7 contributed to the risk of cancer and timing of diagnosis. We may have
8 incomplete exposure ascertainment (and underestimation of duration of use)
9 for part of our cohort since no information was available on prescriptions
10 before July 2005 or over-the-counter use. Yet, potential long-term (protective)
11 effects may be expected to decrease gradually yet significantly after treatment
12 cessation, reducing the potential effect of misclassification on our results due
13 to exposure before 2005. We used the minimal exposure criterion of 180 days
14 to exclude occasional users who are more likely to obtain their NSAIDs over-
15 the-counter, so at a higher price. We did not have data on used daily dosage
16 or duration of use, and used a proxy variable for duration based on
17 accumulation of the average DDDs per package. This explains why some
18 aspirin users had an estimated exposure time longer than the duration of
19 follow-up, indicating a high daily dose. The high variability in actual and
20 estimated administered dosage also hindered assessment of recency of use.
21 Some previous studies subdivided aspirin use into “low dose” and “high dose”
22 based on prescribed dosages (e.g. <75 mg/day[34] or <100 mg/day[14]), but
23 since we did not have information on the number of prescribed pills per day,
24 and different dosages could have been prescribed during the study period, we
25 used the definition based on ATC coding and assessed the estimated
26 duration of use, with the additional advantage that the low-dose aspirin was
27 only available on prescription. This should also be a more accurate reflection
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3 of duration of use than the number of prescriptions.[9] In our study, the DDD
4 per package could range from <5 to 500 (for other NSAIDs) or 1000 (for
5 aspirin), which illustrates the variation between prescriptions. Since 1.4 million
6 individuals were exposed to NSAIDs (≥ 180 days), i.e. one fifth of the adult
7 population in Sweden, our results are likely to be diluted since we compared
8 them with the total background population. Yet, despite this dilution the
9 associations among long-term users were strongly decreased.
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20 Compared to previous studies, this study was better powered to separately
21 analyses different gastrointestinal cancers and types of NSAIDs.[35] The
22 above mentioned meta-analysis[15] identified only 2 cohort studies including
23 over 100,000 individuals assessing colorectal cancer risk among aspirin-
24 users.[36 37] Even our exposed groups for aspirin and non-selective NSAIDs
25 alone were 5-7 times larger than earlier large studies. The decrease in
26 gastrointestinal cancer risk became evident only after longer exposure, which
27 has also been shown in previous research,[15 38] and is biologically plausible
28 given the expected time latency for (hindering) cancer progression.
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42 The higher risk among aspirin and other NSAID users also using PPIs should
43 be interpreted with some caution. PPIs are often prescribed for
44 gastroesophageal reflux and peptic ulcers, which are risk factors for
45 oesophageal and gastric cancer, respectively. Therefore, a higher cancer risk
46 was expected for those locations, yet not for the other gastrointestinal cancer
47 types. PPIs can also be used to prevent peptic ulcers in users of aspirin and
48 other NSAIDs, usually in individuals without any gastro-intestinal morbidity.
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3 Another study of our group based on the same source cohort,[26] investigated
4 the risk of gastric cancer among PPI maintenance users, which suggested an
5 increased risk in all indication groups for PPI (including those without
6 gastrointestinal symptoms); which also supports a potential independent role
7 for PPI in carcinogenesis as also suggested recently by other groups.[39 40]
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9 Together with a potential increased risk of mortality related to long-term PPI
10 use,[41] we believe a more careful approach should be considered when
11 prescribing PPIs to prevent gastrointestinal complications in long-term
12 NSAIDs users. Yet, the risk for gastrointestinal complications such as
13 bleeding should be assessed on an individual bases based on other research
14 investigating shorter-term effects.[42] Before considering implementing aspirin
15 or other NSAIDs as wide-spread intervention, safety, in particular considering
16 long-term use, needs to be considered, with previous research tending
17 towards a “favourable benefit harm-profile” despite an excess risk of
18 bleeding.[43]
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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.

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5 the data and the accuracy of the data analysis. NB conducted and is
6 responsible for the data-analysis. Literature search: NB; Design of the study:
7 both authors; Data collection and preparation for analyses: NB; Data analysis:
8 NB; Data interpretation: both authors; Writing of first draft: NB, revised and
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25 review, or approval of the manuscript.
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34 **Competing interests:** none
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38 **Data sharing statement:** We are willing to share data upon request after
39 ethics approval has been approved by the relevant committee and the
40 governmental agencies that maintain the data.
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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
	<i>Number (%)</i>	<i>Number (%)</i>	<i>Number (%)</i>
Total	783,870	566,209	17,948
Sex			
<i>Men</i>	421,609 (53.8)	210,705 (37.2)	7,201 (40.1)
<i>Women</i>	362,261 (46.2)	355,504 (62.8)	10,747 (59.9)
Age at first prescription			
<i><40 years</i>	12,189 (1.6)	110,592 (19.5)	2,720 (15.2)
<i>40-49 years</i>	32,743 (4.2)	125,977 (22.3)	3,849 (21.5)
<i>50-59 years</i>	108,683 (13.9)	146,981 (26.0)	4,941 (27.5)
<i>60-69 years</i>	200,154 (25.5)	112,682 (19.9)	3,914 (21.8)
<i>≥70 years</i>	430,101 (54.9)	69,977 (12.4)	2,524 (14.1)
Calendar period at first prescription			
<i>2005-2006</i>	557,023 (71.1)	387,443 (68.4)	10,393 (57.9)
<i>2007-2009</i>	156,790 (20.0)	145,208 (25.7)	5,500 (30.6)
<i>2010-2012</i>	70,057 (8.9)	33,558 (5.9)	2,055 (11.5)
Proton pump inhibitors use (≥180 days)			
<i>yes</i>	200,828 (25.6)	148,586 (26.2)	5,602 (31.2)
<i>no</i>	583,042 (74.4)	417,623 (73.8)	12,346 (68.8)
Statins use (≥180 days)			
<i>yes</i>	432,996 (55.2)	77,514 (13.7)	2,589 (14.4)
<i>no</i>	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)
<i>Adenocarcinoma</i>	319 (0.04)	75 (0.01)	4 (0.02)
<i>Squamous cell carcinoma</i>	203 (0.03)	50 (0.01)	2 (0.01)
Gastric cancer	1,079 (0.14)	260 (0.05)	7 (0.04)
<i>Adenocarcinoma</i>	949 (0.12)	212 (0.04)	3 (0.02)
Small bowel cancer	253 (0.03)	94 (0.02)	5 (0.03)
<i>Carcinoid</i>	122 (0.02)	43 (0.01)	2 (0.01)
Colorectal cancer	6,919 (0.88)	2,017 (0.36)	60 (0.33)
<i>Adenocarcinoma</i>	6,608 (0.84)	1,887 (0.33)	59 (0.33)
Liver cancer	645 (0.08)	232 (0.04)	3 (0.02)
<i>Hepatocellular carcinoma</i>	358 (0.05)	100 (0.02)	1 (0.01)
<i>Cholangiocellular carcinoma</i>	81 (0.01)	41 (0.01)	0 (0.00)
Gallbladder and biliary tract cancer	385 (0.05)	190 (0.03)	5 (0.03)
<i>Adenocarcinoma</i>	288 (0.04)	149 (0.03)	2 (0.01)
Pancreatic cancer	1,114 (0.14)	490 (0.09)	13 (0.07)
<i>Adenocarcinoma</i>	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			
<i>Total</i>	3,776,237	3,376,275	82,733
<i>Mean (standard deviation)</i>	4.82 (2.40)	5.96 (1.67)	4.61 (2.21)

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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)
<i>Men</i>	6,659	1.24 (1.21-1.27)	1,390	0.78 (0.74-0.82)
<i>Women</i>	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)
<i>Adenocarcinoma</i>	319	1.17 (1.04-1.30)	75	0.81 (0.64-1.01)
<i>Squamous cell carcinoma</i>	203	1.06 (0.92-1.22)	50	0.66 (0.49-0.87)
<i>Men</i>	415	1.09 (0.99-1.20)	90	0.88 (0.63-0.97)
<i>Women</i>	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)
<i>Adenocarcinoma</i>	949	1.07 (1.00-1.14)	212	0.66 (0.58-0.76)
<i>Men</i>	714	1.08 (1.00-1.16)	128	0.72 (0.60-0.85)
<i>Women</i>	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)
<i>Carcinoid</i>	122	1.11 (0.92-1.32)	43	0.84 (0.61-1.13)
<i>Men</i>	150	1.05 (0.89-1.23)	34	0.72 (0.50-1.00)
<i>Women</i>	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)
	<i>Adenocarcinoma</i>	6,608	1.00 (0.80-1.03)	1,887	0.74 (0.70-0.77)
	<i>Men</i>	4,105	1.03 (1.00-1.06)	793	0.73 (0.68-0.79)
	<i>Women</i>	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)
	<i>Hepatocellular carcinoma</i>	358	1.13 (1.02-1.25)	100	0.83 (0.77-1.01)
	<i>Cholangiocellular carcinoma</i>	81	1.14 (0.91-1.42)	41	1.10 (0.79-1.49)
	<i>Men</i>	449	1.12 (1.02-1.23)	130	1.00 (0.84-1.19)
	<i>Women</i>	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)
	<i>Adenocarcinoma</i>	288	0.93 (0.82-1.04)	149	1.07 (0.90-1.25)
	<i>Men</i>	181	1.00 (0.86-1.15)	50	0.98 (0.73-1.29)
	<i>Women</i>	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)
	<i>Adenocarcinoma</i>	835	1.00 (0.93-1.07)	402	1.02 (0.92-1.13)
	<i>Men</i>	629	1.07 (0.99-1.16)	163	0.89 (0.76-1.03)
	<i>Women</i>	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)

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

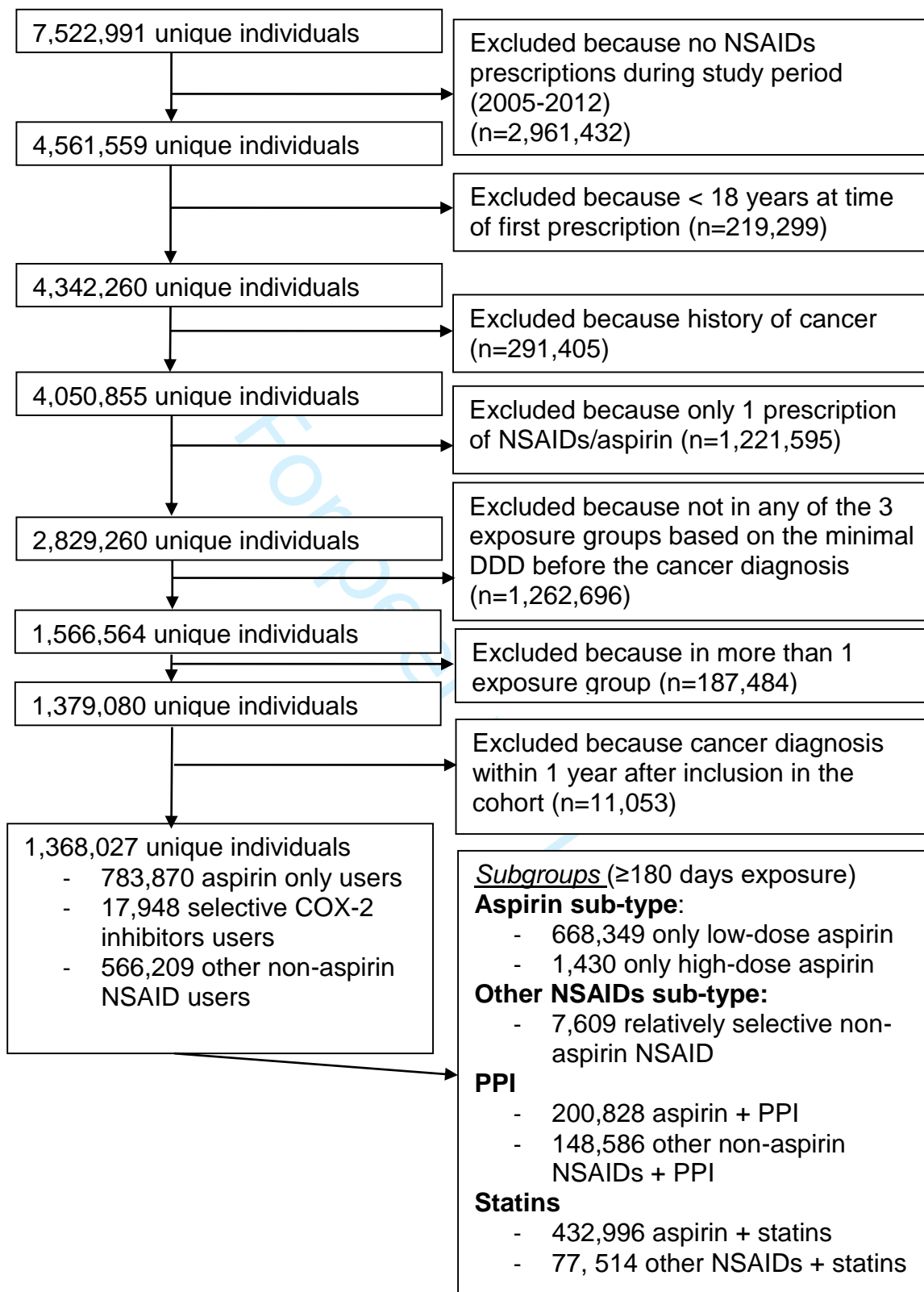
	Aspirin users (n=783,870)		Aspirin with PPI (n=200,828)		Aspirin with statins (n=432,996)	
	<i>Number of cases</i>	<i>SIRS (95% CI)</i>	<i>Number of cases</i>	<i>SIRS (95% CI)</i>	<i>Number of cases</i>	<i>SIRS (95% CI)</i>
All gastrointestinal cancer	10,969	1.02 (1.00-1.04)	3,617	1.25 (1.21-2.29)	6,210	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)	
	<i>Number of cases</i>	<i>SIRS (95% CI)</i>	<i>Number of cases</i>	<i>SIRS (95% CI)</i>	<i>Number of cases</i>	<i>SIRS (95% CI)</i>
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.

For peer review only



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

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2 This cohort included all individuals residing in Sweden who received at least one
3
4 dispensed prescription of one of the following commonly prescribed drugs between July 1,
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6 2005 and December 31, 2014 (with corresponding ATC codes) with follow-up for cancer
7
8 until December 2012: sex hormones (G03), drugs for peptic ulcers and gastro-esophageal
9
10 reflux disease (A02B), acetylsalicylic acid (B01AC06, N02BA), non-steroidal anti-
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12 inflammatory drugs (M01A), HMG CoA reductase inhibitors (C10AA), drugs affecting bone
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14 structure and mineralization, (M05B), and antibiotics (J01AA, J01CA04, J01FA, J01MA,
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16 J01XD, J01XE, J04AB04). This cohort included approximately 85% of all Swedish
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18 residents, with especially high coverage of adults.
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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
	<i>N (%)</i>	<i>N (%)</i>
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

For peer review only

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		Relatively selective COX-2		Low-dose aspirin	
	maintenance users (n=17,948)		inhibitors maintenance users (n=7,609)		(n=668,305)	
	<i>Number</i>		<i>Number</i>		<i>Number</i>	
	<i>of cases</i>	<i>SIRS (95% CI)</i>	<i>of cases</i>	<i>SIRS (95% CI)</i>	<i>of cases</i>	<i>SIRS (95% CI)</i>
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).

	Non-selective			
	Aspirin with PPI vs. without	Aspirin with statin vs. without	non-aspirin NSAIDs with PPI vs. without	Non-selective non-aspirin NSAIDs with statins vs. without
	<i>IRR (95% CI)</i>	<i>IRR (95% CI)</i>	<i>IRR (95% CI)</i>	<i>IRR (95% CI)</i>
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

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3 **Maintenance use of non-steroidal anti-inflammatory drugs**
4
5 **and risk of gastrointestinal cancer in a nationwide population-**
6
7 **based cohort study in Sweden.**
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10 **Running title: NSAIDs and gastrointestinal cancer prevention**

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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

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3 were using PPIs, had higher risks for all gastrointestinal cancer types; and
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5 lower risk if using statins.
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7 **Conclusion:** Long-term use of (low-dose) aspirin and non-selective NSAIDs
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9 was associated with a decreased risk of all gastrointestinal cancer types.
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13 **Key words:** gastro-intestinal cancer, chemoprevention, non-steroidal anti-
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15 inflammatory drugs, aspirin, coxibs, cancer, pharmaco-epidemiology.
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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

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3 of cardiovascular morbidity for COX-2 selective inhibitors compared to
4 nonselective COX-inhibitors.[3 7 8] Some of the older NSAIDs are “relatively
5 selective COX-2 inhibitors”, i.e. nabumetone, meloxicam, etodolac and
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7 nimesulide.[3]
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11 However, epidemiological evidence to support a chemopreventive effect is still
12 limited, mainly because large numbers are needed with a long follow-up, in
13 particular for relatively rare cancer types. Meta-analyses have pooled the
14 evidence of the gastrointestinal cancer preventive potential of aspirin and
15 other NSAIDs.[9-14] A large meta-analysis[15] and another detailed scientific
16 assessment[16] concluded that a preventive effect on colorectal cancer was
17 especially pronounced in daily and long-term users (>5 years) in both
18 interventional and observational studies,[15 16] with similar findings in recent
19 studies on gastric cancer.[17 18] Yet, these studies used several different
20 definitions of exposure, ranging from a single prescription of aspirin to daily
21 use for >5 years, with too few studies reporting stratified analyses per dosage
22 (or indication e.g. low dose anti-coagulants versus high dose analgesics) to
23 draw reliable conclusions (although low dose has been recommended by
24 individual studies).[15] The statistical power was too low to identify
25 associations with many other types of (gastro-intestinal) cancer, and more,
26 large original studies are needed to assess the potential preventive effect of
27 other NSAIDs.[15]
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31 The role of PPI use on the association between NSAIDs with gastrointestinal
32 cancer is insufficiently understood yet increasingly investigated, with growing
33 evidence of carcinogenic and other long-term side-effects of PPIs[19-22] as
34 also shown by our group.[23-25]
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3 The objective of this study was to assess the association of aspirin and other
4 NSAIDs on the risk of different gastrointestinal cancer types, while also
5 assessing the potential influence of concomitant PPI use.
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11 **Material and Methods**

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14 This nationwide Swedish population-based cohort study assessed the risk of
15 gastrointestinal cancer in adult NSAIDs users,[26] compared to the risk in the
16 entire Swedish background population of the corresponding sex, age and
17 calendar year (7.1-7.6 million adults) as provided by Statistics Sweden. [27]
18 [27] [27] Participants were enrolled during the study period from July 1, 2005
19 (the start of the Swedish Prescribed Drug Registry) to December 31, 2012, as
20 described in more detail elsewhere.[23 25 28 29] The cohort members were
21 followed up until the occurrence of any cancer (excluding non-melanoma skin
22 cancer), death or December 31, 2012 (i.e. the end of data collection for the
23 Swedish Cancer Registry), whichever occurred first. Individuals with a history
24 of any cancer were excluded, as well as individuals with a cancer diagnosis
25 within 12 months after inclusion (to avoid reverse causation). The unique 10-
26 digit personal identity number, assigned to each Swedish resident, was used
27 for identification of all participants and for linkages of their individual data
28 between registries. This study was conducted according to a detailed and a-
29 priori established study protocol.
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51 **Data collection**

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53 The data for the present study were derived from our Chemoprevention of
54 cancer cohort. The study protocol conforms to the ethical guidelines of the
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3 1975 Declaration of Helsinki as reflected in a prior approval by the institution's
4 human research committee, the Regional Ethical Review Board in Stockholm,
5 without need for informed consent (2014/1291-31/4, approved 27 AUG
6 2014)(see Supplement 1 and [25 26 30]). This data collection originates from
7 the nationwide complete Swedish Prescribed Drug Registry, and includes all
8 individuals residing in Sweden who have collected at least one dispensed
9 prescription of any commonly prescribed drug between July 1, 2005 and
10 December 31, 2014 (approximately 85% of all Swedish residents); with follow-
11 up for cancer until December 31, 2012. This cohort has been linked to two
12 other high-quality and complete nationwide Swedish registries, i.e. the
13 Swedish Cancer Registry (>96% completeness of all cancers, originated in
14 1961),[31] and the Swedish Causes of Death Registry (>99% completeness,
15 originated in 1952), by means of the personal identity number.
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33 **Exposures**

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35 Therapy with systemic NSAIDs was defined as at least 6 months (≥ 180 days)
36 cumulative exposure during the study period. This was a cumulative exposure
37 based on the defined daily dosage (DDD) per prescribed package, which
38 takes into account the potency of the drug as well as the prescribed quantity.
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40 Three main types of NSAIDs were categorized based on their mechanisms of
41 action (selective or non-selective COX inhibition) and drug class (aspirin or
42 non-aspirin NSAIDs) with corresponding Anatomical Therapeutic Chemical
43 classification codes (ATC): 1) aspirin (B01AC06, N02BA), 2) selective COX-2
44 inhibitors (coxibs, M01AH), and 3) non-selective non-aspirin NSAIDs
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46 (remaining M01A codes). Individuals with ≥ 180 days of exposure to 2 or 3 of
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3 these groups were excluded, so the 3 groups are mutually exclusive. Users of
4 combination preparations including aspirin, i.e. with corticosteroid (M01BA03),
5 PPIs (B01AC56), statins (C10BX), as well as preparations for local (oral) use
6 (A01AD05) were also excluded.

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11 Additionally, the relatively selective COX-2 inhibitors, a subgroup of the non-
12 selective NSAID users, containing meloxicam (M01AC06) and nabumetone
13 (M01AX01), were also analysed separately. Aspirin users were also divided in
14 2 groups according to their ATC code (≥ 180 days): low dose (B01AC06), and
15 high dose aspirin (N02BA) (those using both for ≥ 180 days were
16 excluded).[32] High-dose aspirin (N02BA) and some other NSAIDs
17 (Diclofenac, M01AB05 and Ibuprofen, M01AE01) are also available over the
18 counter in Sweden, but they are sold in only small packages and at higher
19 prices per dose.[32 33] Thus, we can assume that maintenance users had
20 their doses prescribed, and were thus recorded in the present study.
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35 **Outcomes**

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37 The outcome was a first gastrointestinal cancer diagnosis recorded in the
38 Swedish Cancer Registry according to the International Classification of
39 Diseases (ICD) 10th edition, including all cancers of the alimentary and
40 hepatobiliary tract. Gastrointestinal cancers were categorized as follows: any
41 gastrointestinal cancer (C15-C26) or cancer of the oesophagus (C15),
42 stomach (C16), small bowel (C17), colorectum (C18-C21), liver, including
43 intrahepatic bile ducts (C22), gallbladder or extrahepatic bile ducts (C23-24),
44 or pancreas (C25). The category “other gastrointestinal cancer” (C26) was not
45 analysed separately. Additionally, the most common histological tumour types
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3 were analysed separately: adenocarcinoma (code 096) for oesophageal,
4 gastric, gallbladder/biliary tract, pancreas and colorectal cancer; squamous
5 cell carcinoma (code 146) for oesophageal cancer; hepatocellular carcinoma
6 (code 066) and cholangiocarcinoma (code 076) for liver cancer; and carcinoid
7 (code 086) for small bowel cancer.
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17 **Statistical analyses**

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19 The relative risks of developing gastrointestinal cancer in individuals exposed
20 to the drugs under study were standardized using the Swedish background
21 population of the corresponding age, sex, and calendar period. Standardized
22 incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated,
23 while accounting for changes in age and calendar categories when calculating
24 years of follow-up.[34] Follow-up time was counted from the dispense date of
25 the first NSAID prescription to the date of a first cancer diagnosis, death, or
26 the end of the study (31st December 2012), whichever occurred first. The
27 expected incidence rates were calculated from cancer data recorded in the
28 Swedish Cancer Registry and the age-stratified number of individuals per
29 calendar year according to Statistics Sweden (Population Statistics). The
30 overall SIR for gastrointestinal cancer was calculated, as well as SIRs for
31 each anatomical location separately, including sub-analyses for the most
32 common histological types. The analyses were also stratified for sex and age
33 for each cancer type. Subgroup analyses were performed for high-dose and
34 low-dose aspirin, users of relatively selective COX-2 inhibitors, NSAID use
35 with concurrent PPI (A02BC) or statin (C10AA) use (≥ 180 days) if the groups
36 were sufficiently large. To assess the effect of PPI and statins, a multivariable
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3 Poisson regression model was fitted, adjusting for age at first prescription, sex
4 and interaction between PPI and statins, and presented as incidence rate
5 ratios (IRR) and 95%CI. The duration of the exposures was assessed by
6 dividing the total cumulative dosage (sum of DDDs per package) received
7 before the cancer diagnosis into four equally sized groups (quartiles), yet their
8 total follow-up time was taken into account for the analyses. There were no
9 missing data on exposures, outcomes or confounding variables. Effect
10 estimates were only reported when at least 5 individuals developed the
11 outcome.
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24 ***Patient involvement***

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

44 Among all 1,368,027 users of NSAIDs, there were 783,870 (57.3%) aspirin
45 users, 566,209 (41.4%) non-selective NSAIDs users, and 17,948 (1.3%)
46 COX-2 users (Table 1, Supplement 1). Aspirin users were more likely to be
47 male (53.8%) and older than 70 years (54.9.2%), while non-selective NSAID
48 users and COX-2 users were predominantly female (62.8% and 59.9%,
49 respectively) and between 40 and 70 years of age (68.2% and 70.8%,
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3 respectively). Use of PPIs was found in 25.6%, 26.2%, and 31.2% of the
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5 aspirin users, non-selective NSAIDs users, and COX-2 users, respectively;
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7 and use of statins in 55.2%, 13.7% and 14.4%, respectively. The majority of
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9 the population received their first prescription during the first half year of the
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11 study period (2005), 54.9% of aspirin users, and 42.5% of non-selective
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13 NSAIDs users (Supplement 2).
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16 17 18 **Aspirin**

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20 As presented in Table 1, 10,969 (1.40%) aspirin users developed some type
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22 of gastrointestinal cancer during the follow-up. The most common cancer sites
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24 were colorectal (n=6,919; 0.88%), gastric (n=1,079; 0.14%), and pancreatic
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26 (n=1,114; 0.14%). There was no association with gastrointestinal cancer
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28 based on the overall SIRs for aspirin users (SIR=1.02, 95% CI 1.00-1.04)
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30 (Table 2). Shorter duration of use (<5.5 years) seemed to be associated with
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32 an increased risk for all gastro-intestinal cancers. Yet, longer duration of
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34 aspirin use was followed by a decreased SIR for gastrointestinal cancer
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36 (SIR=0.31, 95% CI 0.30-0.33 for those with an estimated use between 5.5-7.7
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38 years, and SIR=0.37, 95%CI 0.35-0.40 for >7.7 years) (Table 3) and long-
39
40 term aspirin users had clearly decreased SIRs for each gastrointestinal
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42 cancer type (Table 3). The subgroup analyses including only the low-dosage
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44 aspirin users (N=668,305, 85.3% of the aspirin cohort) showed lower SIRs for
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46 all cancer locations, with significantly reduced risks for all locations except for
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48 oesophageal, gastric and liver cancer (Supplement 3).
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54 55 **Non-selective NSAIDs**

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3 Table 1 shows that 3,428 (0.61%) of the non-selective NSAID users
4 developed cancer, mainly colorectal (n=2,017; 0.36%), pancreatic (n=490;
5 0.09%), and gastric cancers (n=260; 0.05%). Overall, there was a decreased
6 risk of gastrointestinal cancer (SIR=0.79, 95%CI 0.77-0.82), and also for
7 gastric (SIR=0.70, 95% CI 0.62-0.80), colorectal (SIR=0.74, 95% CI 0.71-
8 0.77) and oesophageal (SIR=0.75, 95% CI 0.63-0.89) cancers analysed
9 separately (and their main histological subtypes) (Table 2). There was no
10 evidence of decreased SIRs for the other types of gastrointestinal cancer
11 types, although the effect sizes indicated a decreased SIR of small bowel and
12 liver cancer. Longer duration of use of non-selective NSAIDs was associated
13 with a decreased gastrointestinal cancer risk for all anatomical locations
14 (Table 3).
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31 **Selective COX-2 inhibitors**

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

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50 Among the non-selective NSAIDs users, 7,609 individuals used relatively
51 selective COX-2 inhibitors, of whom 74 (0.01%) developed cancer. There was
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3 no evidence for an association with any of the gastrointestinal cancer
4 locations (Supplement 3).
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8 9 ***Aspirin with PPIs or statins***

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11 Users of aspirin with concomitant use of PPIs had higher SIRs for all
12 gastrointestinal cancers compared to those not using PPIs, with all SIRs
13 indicating an increased risk except for gallbladder cancer (Table 4). The SIRs
14 were especially increased for gastric cancer (SIR=1.89; 95% CI 1.73-2.06)
15 and oesophageal cancer (SIR=1.94; 95% CI 1.71-2.20). When using Poisson
16 regression to compare aspirin users using PPIs directly with aspirin users not
17 using PPIs (instead of using the background population as reference), the risk
18 was increased for all gastrointestinal cancers (IRR=1.19, 95% CI 1.11-1.26),
19 with significantly increased risks for oesophageal, gastric, small bowel, liver
20 and pancreatic cancer (Supplement 4).
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33 Among aspirin users exposed to statins, the SIRs were close to unity for each
34 anatomical location (Table 4). When aspirin users using statins were directly
35 compared with aspirin users not using statins, risks were decreased for all
36 gastrointestinal cancers (IRR=0.81, 95% CI 0.77-0.85), with significant
37 decreases for all cancer locations except for colorectal and pancreatic cancer
38 (Supplement 4).
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48 ***Non-selective NSAIDs with PPIs or statins***

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50 In users of non-selective NSAIDs on therapy with PPIs, the SIRs were
51 increased for all gastrointestinal cancer types (and again higher than among
52 those not using PPIs), except for colorectal cancer (Table 4). When users of
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3 non-selective NSAIDs using PPIs were directly compared with those not using
4 PPIs, risks were increased for all gastrointestinal cancers (IRR=1.61, 95% CI
5 1.49-1.74), and each individual cancer location except for gallbladder cancer
6 (Supplement 4). Among non-selective NSAIDs users using statins, the SIRs
7 were lower than among all users of non-selective NSAIDs, and significantly
8 reduced for oesophageal, gastric and colorectal cancer. When users of non-
9 selective NSAIDs using statins were directly compared with those not using
10 statins, risks were decreased for all gastrointestinal cancers (IRR=0.86, 95%
11 CI 0.76-0.96), yet not significant for the individual cancer locations
12 (Supplement 4).
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27 **Discussion**

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29 This study on contemporary use of NSAIDs showed a decreased risk of all
30 types of gastrointestinal cancer among long-term users of aspirin (>5.5 years)
31 and non-selective NSAIDs users even for shorter duration of use (>0.7 years).
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33 Long-term users of non-selective NSAIDs were at a particularly decreased
34 risk for gastric, oesophageal, and colorectal cancers. These seemingly
35 protective associations might be counteracted by concomitant PPI therapy,
36 and enhanced by concomitant statin use.
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47 The main strengths of this study are the population-based design and large
48 sample size, including all adults residing in Sweden during the study period,
49 which enabled separate analyses for contemporary use of different types of
50 NSAIDs, and evaluation of less common types of gastrointestinal cancer
51 which could not be assessed previously because of insufficient power, in
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3 particular for non-aspirin NSAIDs. Other advantages include the complete
4 follow-up and accurate censoring for mortality. The data on the exposures
5 (medications) and outcomes (gastrointestinal cancers) were highly accurate
6 due to the validity and completeness of the Swedish registries, eliminating
7 recall bias.
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15 Although our findings for aspirin are largely consistent with the literature, that
16 the protective effect is only seen after 5 years, reverse causation, confounding
17 and/or bias appear to influence the aspirin analyses because of the apparent
18 initial increased risk of cancer among short-term users. By excluding all
19 individuals diagnosed with cancer within a year after enrolment, and only
20 including those with a minimal accumulated duration of use of 6 months, the
21 risk of reverse causation should be reduced. Yet, our results indicate that
22 those with an estimated duration shorter than 5 years have an apparent
23 increased risk, which might be because they take aspirin because of yet
24 undiagnosed cancer-related pain or thrombotic events – indicating
25 confounding by indication and reverse causation among the group with the
26 shortest exposure time, an effect which could not have been detected in
27 intervention trials or in case-control studies with a study-design-inherent more
28 restrictive selection of study participants.[15 35] As previous studies reported,
29 15-20% of cancer patients have thrombotic complications during the course of
30 the disease (often as early manifestation of an occult malignancy),[36] yet
31 these complications (e.g. deep venous thrombosis) are more likely to be
32 treated with anti-coagulants than aspirin. However, when only looking at those
33 exclusively using low-dose aspirin for ≥ 180 days, i.e. the platelet aggregation
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3 inhibitors, the protective effects were also visible in the overall analyses non
4 taking into account duration, with SIR=0.86 (95%CI 0.85-0.88). This indicates
5 that the apparent increased risks are mainly because of the small group using
6 aspirin as analgesic (high dose), which shows it is important to distinguish
7 between both groups of aspirin-use. Reverse causality seems to be less of a
8 problem for other NSAIDs users, although these may be used as
9 analgesics.[37] Yet, individuals using NSAIDs may be at a lower a-priori risk
10 of developing gastro-intestinal cancer, because individuals with upper gastro-
11 intestinal symptoms are less likely to be chronic NSAIDs users due to the risk
12 of gastro-intestinal side-effects.

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

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46 Another limitation is potential confounding, e.g. by socio-economic status,
47 dietary factors, obesity, tobacco smoking, and alcohol consumption, which
48 could not be taken into account since such information was not available for
49 the total background population. However, we adjusted for age, sex and
50 calendar period. Cancer-type specific confounders and their treatment such
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3 as *Helicobacter pylori* for gastric cancer, hepatitis B/C infection for liver cancer
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5 and chronic inflammatory diseases such as inflammatory bowel disease for
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7 bowel cancer and pancreatitis for pancreatic cancer, may also have
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9 contributed to the risk of cancer and timing of diagnosis. We may have
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11 incomplete exposure ascertainment (and underestimation of duration of use)
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13 for part of our cohort since no information was available on prescriptions
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15 before July 2005 or over-the-counter use. Yet, potential long-term (protective)
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17 effects may be expected to decrease gradually yet significantly after treatment
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19 cessation, reducing the potential effect of misclassification on our results due
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21 to exposure before 2005. We used the minimal exposure criterion of 180 days
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23 to exclude occasional users who are more likely to obtain their NSAIDs over-
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25 the-counter, so at a higher price. We did not have data on used daily dosage
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27 or duration of use, and used a proxy variable for duration based on
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29 accumulation of the average DDDs per package. This explains why some
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31 aspirin users had an estimated exposure time longer than the duration of
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33 follow-up, indicating a high daily dose. The high variability in actual and
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35 estimated administered dosage also hindered assessment of recency of use.
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37 Some previous studies subdivided aspirin use into “low dose” and “high dose”
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39 based on prescribed dosages (e.g. <75 mg/day[38] or <100 mg/day[14]), but
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41 since we did not have information on the number of prescribed pills per day,
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43 and different dosages could have been prescribed during the study period, we
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45 used the definition based on ATC coding and assessed the estimated
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47 duration of use, with the additional advantage that the low-dose aspirin was
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49 only available on prescription. This should also be a more accurate reflection
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51 of duration of use than the number of prescriptions.[9] In our study, the DDD
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3 per package could range from <5 to 500 (for other NSAIDs) or 1000 (for
4 aspirin), which illustrates the variation between prescriptions. Since 1.4 million
5 individuals were exposed to NSAIDs (≥ 180 days), i.e. one fifth of the adult
6 population in Sweden, our results are likely to be diluted since we compared
7 them with the total background population. Yet, despite this dilution the
8 associations among long-term users were strongly decreased.
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18 Compared to previous studies, this study was better powered to separately
19 analyses different gastrointestinal cancers and types of NSAIDs.[39] The
20 above mentioned meta-analysis[15] identified only 2 cohort studies including
21 over 100,000 individuals assessing colorectal cancer risk among aspirin-
22 users.[40 41] Even our exposed groups for aspirin and non-selective NSAIDs
23 alone were 5-7 times larger than earlier large studies. The decrease in
24 gastrointestinal cancer risk became evident only after longer exposure, which
25 has also been shown in previous research,[15 42] and is biologically plausible
26 given the expected time latency for (hindering) cancer progression.
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39 The higher risk among aspirin and other NSAID users also using PPIs should
40 be interpreted with some caution. PPIs are often prescribed for
41 gastroesophageal reflux and peptic ulcers, which are risk factors for
42 oesophageal and gastric cancer, respectively. Therefore, a higher cancer risk
43 was expected for those locations, yet not for the other gastrointestinal cancer
44 types. PPIs can also be used to prevent peptic ulcers in users of aspirin and
45 other NSAIDs, usually in individuals without any gastro-intestinal morbidity.
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54 Two other studies of our group based on the same source cohort,[23 25]
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3 investigated the risk of gastric and oesophageal cancer among PPI
4 maintenance users, which suggested an increased risk in all indication groups
5 for PPI (including those without gastrointestinal symptoms, and aspirin/NSAID
6 users); which also supports a potential independent role for PPI in
7 carcinogenesis as also suggested recently by other groups.[43 44] Together
8 with a potential increased risk of mortality related to long-term PPI use,[45] we
9 believe a more careful approach should be considered when prescribing PPIs
10 to prevent gastrointestinal complications in long-term NSAIDs users. Yet, the
11 risk for gastrointestinal complications such as bleeding should be assessed
12 on an individual bases based on other research investigating shorter-term
13 effects.[46] Before considering implementing aspirin or other NSAIDs as wide-
14 spread intervention, safety, in particular considering long-term use, needs to
15 be considered, with previous research tending towards a “favourable benefit
16 harm-profile” despite an excess risk of bleeding.[47]
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35 To conclude, this large Swedish nationwide and population-based cohort
36 study on contemporary and long-term use of NSAIDs indicates a strongly
37 protective effect of long-term use of both (low-dose) aspirin and other non-
38 selective NSAIDs on gastrointestinal cancer development.
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3 **Authors' contributions:** NB is the submission guarantor. NB and JL had full
4 access to all the data in the study and take responsibility for the integrity of
5 the data and the accuracy of the data analysis. NB conducted and is
6 responsible for the data-analysis. Literature search: NB; Design of the study:
7 both authors; Data collection and preparation for analyses: NB; Data analysis:
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25 review, or approval of the manuscript.
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34 **Competing interests:** none
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38 **Data sharing statement:** We are willing to share data upon request after
39 ethics approval has been approved by the relevant committee and the
40 governmental agencies that maintain the data.
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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
	<i>Number (%)</i>	<i>Number (%)</i>	<i>Number (%)</i>
Total	783,870	566,209	17,948
Sex			
<i>Men</i>	421,609 (53.8)	210,705 (37.2)	7,201 (40.1)
<i>Women</i>	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)			
<i>yes</i>	200,828 (25.6)	148,586 (26.2)	5,602 (31.2)
<i>no</i>	583,042 (74.4)	417,623 (73.8)	12,346 (68.8)
Statins use (≥180 days)			
<i>yes</i>	432,996 (55.2)	77,514 (13.7)	2,589 (14.4)
<i>no</i>	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)
<i>Adenocarcinoma</i>	319 (0.04)	75 (0.01)	4 (0.02)
<i>Squamous cell carcinoma</i>	203 (0.03)	50 (0.01)	2 (0.01)
Gastric cancer	1,079 (0.14)	260 (0.05)	7 (0.04)
<i>Adenocarcinoma</i>	949 (0.12)	212 (0.04)	3 (0.02)
Small bowel cancer	253 (0.03)	94 (0.02)	5 (0.03)
<i>Carcinoid</i>	122 (0.02)	43 (0.01)	2 (0.01)
Colorectal cancer	6,919 (0.88)	2,017 (0.36)	60 (0.33)
<i>Adenocarcinoma</i>	6,608 (0.84)	1,887 (0.33)	59 (0.33)
Liver cancer	645 (0.08)	232 (0.04)	3 (0.02)
<i>Hepatocellular carcinoma</i>	358 (0.05)	100 (0.02)	1 (0.01)
<i>Cholangiocellular carcinoma</i>	81 (0.01)	41 (0.01)	0 (0.00)
Gallbladder and biliary tract cancer	385 (0.05)	190 (0.03)	5 (0.03)
<i>Adenocarcinoma</i>	288 (0.04)	149 (0.03)	2 (0.01)
Pancreatic cancer	1,114 (0.14)	490 (0.09)	13 (0.07)
<i>Adenocarcinoma</i>	835 (0.11)	402 (0.07)	11 (0.06)

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3	Other gastrointestinal cancer	35 (0.00)	11 (0.00)	0 (0.00)
4	Duration of follow-up in person-years			
5	<i>Total</i>	3,776,237	3,376,275	82,733
6	<i>Mean (standard deviation)</i>	4.82 (2.40)	5.96 (1.67)	4.61 (2.21)
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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)
<i>Men</i>	6,659	1.24 (1.21-1.27)	1,390	0.78 (0.74-0.82)
<i>Women</i>	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)
<i>Adenocarcinoma</i>	319	1.17 (1.04-1.30)	75	0.81 (0.64-1.01)
<i>Squamous cell carcinoma</i>	203	1.06 (0.92-1.22)	50	0.66 (0.49-0.87)
<i>Men</i>	415	1.09 (0.99-1.20)	90	0.88 (0.63-0.97)
<i>Women</i>	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)
<i>Adenocarcinoma</i>	949	1.07 (1.00-1.14)	212	0.66 (0.58-0.76)
<i>Men</i>	714	1.08 (1.00-1.16)	128	0.72 (0.60-0.85)
<i>Women</i>	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)
<i>Carcinoid</i>	122	1.11 (0.92-1.32)	43	0.84 (0.61-1.13)
<i>Men</i>	150	1.05 (0.89-1.23)	34	0.72 (0.50-1.00)
<i>Women</i>	103	1.06 (0.86-1.28)	60	0.93 (0.71-1.19)
18-39 years	0	-	1	-
40-49 years	1	-	3	-

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2		50-59 years	18	1.53 (0.91-2.41)	18	0.77 (0.46-1.22)
3		60-69 years	64	1.16 (0.89-1.48)	33	0.81 (0.56-1.14)
4		≥70 years	170	0.99 (0.85-1.15)	39	0.98 (0.69-1.34)
5						
6	Colorectal cancer		6,919	1.00 (0.98-1.03)	2,017	0.74 (0.71-0.77)
7		<i>Adenocarcinoma</i>	6,608	1.00 (0.80-1.03)	1,887	0.74 (0.70-0.77)
8		Men	4,105	1.03 (1.00-1.06)	793	0.73 (0.68-0.79)
9		Women	2,814	0.97 (0.93-1.00)	1,224	0.74 (0.70-0.78)
10		18-39 years	2	-	10	0.61 (0.29-1.13)
11		40-49 years	9	0.52 (0.24-0.98)	51	0.47 (0.35-0.62)
12		50-59 years	241	1.16 (1.02-1.31)	232	0.55 (0.48-0.63)
13		60-69 years	1,268	1.05 (0.99-1.11)	600	0.66 (0.60-0.71)
14		≥70 years	5,399	0.99 (0.96-1.02)	1,124	0.88 (0.83-0.94)
15						
16	Liver cancer		645	1.11 (1.03-1.20)	232	0.96 (0.84-1.09)
17		<i>Hepatocellular carcinoma</i>	358	1.13 (1.02-1.25)	100	0.83 (0.77-1.01)
18		<i>Cholangiocellular carcinoma</i>	81	1.14 (0.91-1.42)	41	1.10 (0.79-1.49)
19		Men	449	1.12 (1.02-1.23)	130	1.00 (0.84-1.19)
20		Women	196	1.09 (0.94-1.26)	102	0.91 (0.74-1.10)
21		18-39 years	0	-	3	-
22		40-49 years	4	-	10	0.95 (0.46-1.75)
23		50-59 years	32	1.04 (0.71-1.47)	44	0.90 (0.65-1.21)
24		60-69 years	182	1.36 (1.17-1.57)	90	0.99 (0.79-1.21)
25		≥70 years	427	1.03 (0.94-1.14)	85	0.95 (0.76-1.17)
26						
27	Gallbladder and biliary tract cancer		385	0.92 (0.83-1.01)	190	1.03 (0.89-1.19)
28		<i>Adenocarcinoma</i>	288	0.93 (0.82-1.04)	149	1.07 (0.90-1.25)
29		Men	181	1.00 (0.86-1.15)	50	0.98 (0.73-1.29)
30		Women	204	0.85 (0.74-0.80)	140	1.05 (0.88-1.24)
31		18-39 years	0	-	1	-
32		40-49 years	0	-	7	0.97 (0.39-2.00)
33		50-59 years	6	0.52 (.19-1.13)	12	0.46 (0.24-0.80)
34		60-69 years	91	1.31 (1.05-1.60)	63	1.00 (0.77-1.28)
35		≥70 years	288	0.85 (0.76-0.96)	107	1.23 (1.00-1.48)
36						
37	Pancreatic cancer		1,114	1.04 (0.98-1.11)	490	1.00 (0.92-1.10)
38		<i>Adenocarcinoma</i>	835	1.00 (0.93-1.07)	402	1.02 (0.92-1.13)
39		Men	629	1.07 (0.99-1.16)	163	0.89 (0.76-1.03)
40		Women	485	1.01 (0.92-1.11)	327	1.08 (0.96-1.20)
41		18-39 years	1	-	1	-
42		40-49 years	3	-	26	1.65 (1.08-2.42)
43		50-59 years	37	0.91 (0.64-1.25)	68	0.86 (0.67-1.09)
44		60-69 years	307	1.19 (1.06-1.33)	174	0.85 (0.73-0.99)
45		≥70 years	766	1.00 (0.93-1.07)	221	1.18 (1.03-1.35)
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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)

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

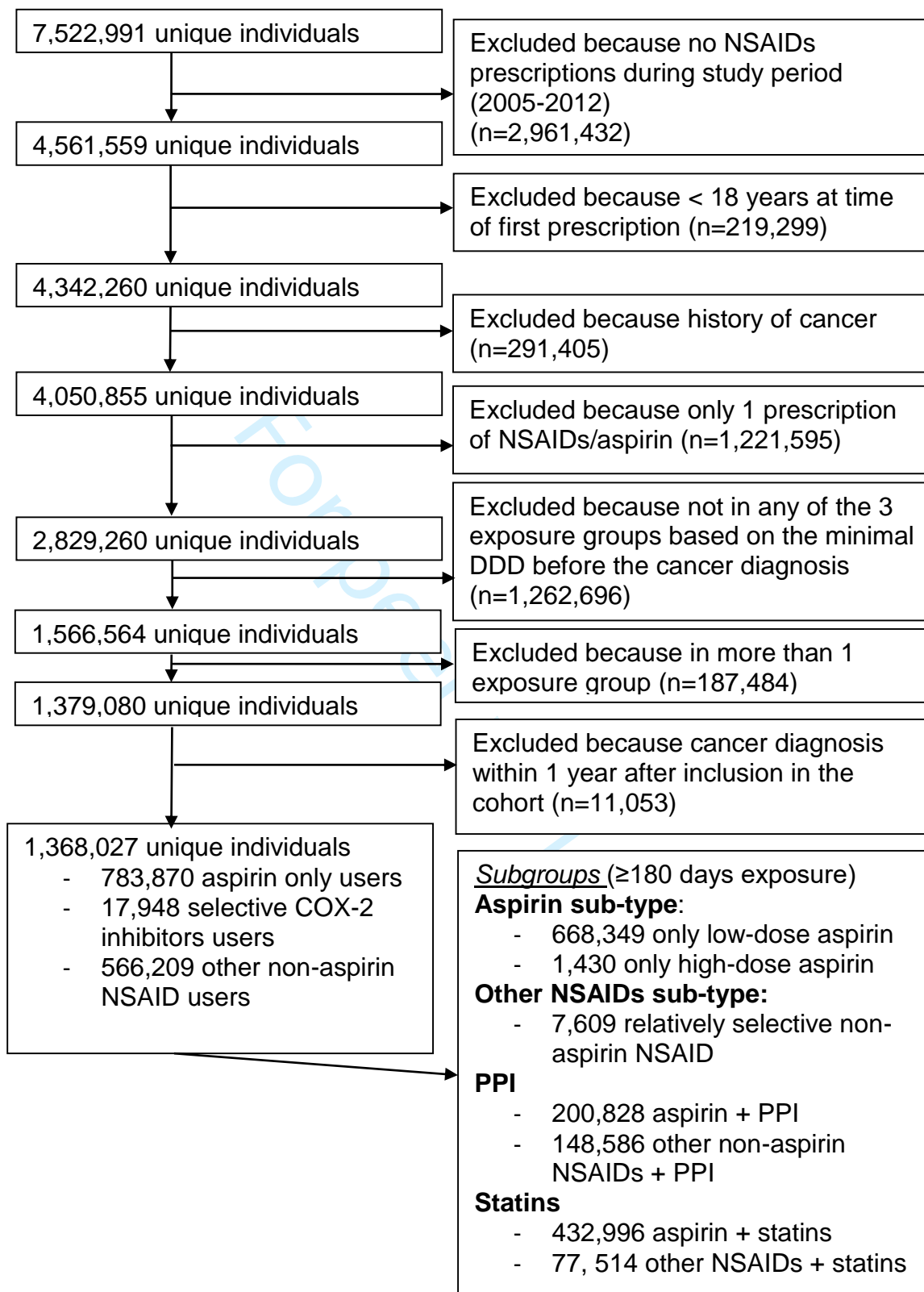
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For peer review only

Online Supplement 1

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

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

1
2 This cohort included all individuals residing in Sweden who received at least one
3
4 dispensed prescription of one of the following commonly prescribed drugs between July 1,
5
6 2005 and December 31, 2014 (with corresponding ATC codes) with follow-up for cancer
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8 until December 2012: sex hormones (G03), drugs for peptic ulcers and gastro-esophageal
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10 reflux disease (A02B), acetylsalicylic acid (B01AC06, N02BA), non-steroidal anti-
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12 inflammatory drugs (M01A), HMG CoA reductase inhibitors (C10AA), drugs affecting bone
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14 structure and mineralization, (M05B), and antibiotics (J01AA, J01CA04, J01FA, J01MA,
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16 J01XD, J01XE, J04AB04). This cohort included approximately 85% of all Swedish
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18 residents, with especially high coverage of adults.
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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
	<i>N (%)</i>	<i>N (%)</i>
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

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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		Relatively selective COX-2		Low-dose aspirin	
	maintenance users (n=17,948)		inhibitors maintenance users (n=7,609)		(n=668,305)	
	<i>Number</i>		<i>Number</i>		<i>Number</i>	
	<i>of cases</i>	<i>SIRS (95% CI)</i>	<i>of cases</i>	<i>SIRS (95% CI)</i>	<i>of cases</i>	<i>SIRS (95% CI)</i>
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).

	Non-selective			
	Aspirin with PPI vs. without	Aspirin with statin vs. without	non-aspirin NSAIDs with PPI vs. without	Non-selective non- aspirin NSAIDs with statins vs. without
	<i>IRR (95% CI)</i>	<i>IRR (95% CI)</i>	<i>IRR (95% CI)</i>	<i>IRR (95% CI)</i>
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>.