Title: Exposure to weak opioids and risk of gastrointestinal tract cancers: A series of nested case-control studies.

Running title: Weak opioids and GI cancer risk

Authors: Martin G Houston MB BCh[1], Úna McMenamin PhD[1], Brian Johnston MD[2], Ronald D McDowell PhD[1], Carmel M Hughes PhD[3], Peter Murchie, PhD[4], Chris R Cardwell PhD[1].

Authors' Institutions:

[1] Centre for Public Health, Queen's University, Grosvenor Rd., Belfast, Co. Antrim, UK, BT12 6BA.

[2] Department of Gastroenterology, Royal Victoria Hospital, Belfast, Co. Antrim, UK, BT12 6BA.

[3] School of Pharmacy, Queen's University, Lisburn Rd, Belfast, Co. Antrim, UK. BT9 7BL.

[4] Institute of Applied Health Sciences Section, Academic Primary Care, Foresterhill, Aberdeen, UK, AB24 2ZD.

Corresponding author:

Dr. Martin Houston, Queen's University Belfast, Centre for Public Health, Institute of Clinical Sciences, Royal Victoria Hospital, Belfast, BT12 6BA. Email: mhouston09@qub.ac.uk.

Acknowledgements:

We wish to thank PCCIUR, University of Aberdeen, especially Artur Wozniak, for extracting the data and performing case-control matching. This work was supported by Cancer Research UK (reference C37316/A25535). ÚMcM is supported by a UKRI Future Leaders Fellowship (MR/T019859/1). The sponsors had no involvement with the planning, execution, or completion of the study.

Guarantor of the article: Dr. Martin Houston is acting as the submission's guarantor.

Author contributions: Funding acquisition: CRC, CMH, PM; data acquisition: CRC, RDM, CMH, PM; study design: MGH, CRC, RDM, CMH, PM; data analysis and interpretation: MGH, CRC, ÚMcM, BJ, RDM, CMH, PM; writing original draft: MGH, CRC; writing, review and editing: MGH, CRC, ÚMcM, BJ, RDM, CMH, PM. All authors approved the final version of the manuscript.

Personal and funding interests: None.

Data availability: The data that support the findings of this study are available from the Institute of Applied Health Sciences, University of Aberdeen. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the Institute of Applied Health Sciences Section.

Word count: **Main text**: 2,487

Abstract: 250

Summary

Background

There is evidence gastrointestinal (GI) motility may play a role in the development of GI cancers. Weak opioids (codeine and dihydrocodeine) decrease GI motility, but their effect on GI cancer risk has not been assessed.

Aim

To assess the association between weak opioids and cancers of the GI tract.

Methods

A series of nested case-control studies was conducted using Scottish general practice records from the Primary Care Clinical Informatics Unit Research database. Oesophageal (n=2,432), gastric (n=1,443), and colorectal cancer (n=8,750) cases, diagnosed between 1999 and 2011, were identified and matched with up to five controls. Weak opioid use was identified from prescribing records. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression, adjusting for relevant comorbidities and medication use.

Results

There was no association between weak opioids and colorectal cancer (adjusted OR=0.96, CI 0.90, 1.02, p=0.15). There was an increased risk of oesophageal (adjusted OR=1.16, CI 1.04, 1.29, p=0.01) and gastric cancer (adjusted OR=1.26, CI 1.10, 1.45, p=0.001). The associations for oesophageal cancer, but not gastric cancer, were attenuated when weak opioid users were compared with users of another analgesic (adjusted OR=1.03 CI 0.86, 1.22, p=0.76 and adjusted OR=1.29 CI 1.02, 1.64, p=0.04 respectively).

Conclusion

In this large population-based study, there was no consistent evidence of an association between weak opioids and oesophageal or colorectal cancer risk, but a small increased risk of gastric cancer. Further investigation is required to determine whether this association is causal or reflects residual confounding or confounding by indication.

Keywords:

Opioids, Codeine, Dihydrocodeine, Gastrointestinal neoplasms, Oesophageal cancer, Gastric cancer, Colorectal cancer, Gastrointestinal motility.

1 Introduction

Gastrointestinal (GI) motility may play a role in the development of GI tract cancers. A recent, large Danish cohort study has demonstrated increased risk of various GI tract cancers in patients diagnosed with constipation. Although there was no long-term risk of colorectal cancer, an increased risk of oesophageal, stomach, small intestine, liver, and pancreatic cancer was observed after 15 years of follow-up.[1] Meta-analysis of observational studies has provided conflicting evidence on the role of constipation and colorectal cancer risk.[2] Regular exercise is associated with reduced GI cancer risk, potentially due to decreased GI transit time and subsequent reduced carcinogen exposure to GI mucosa. Several studies have demonstrated exercise also beneficially modifies the GI microbiome, although the underlying mechanisms remain unknown.[3] Decreased GI motility due to opioid use has been

associated with decreased GI mucosal integrity and subsequent dysbiosis,[4] which is implicated in the development of GI cancers.[5] Further, there is experimental evidence that delayed gastric emptying increases risk of gastric cancer in murine models. Mice who underwent vagotomy (which delays gastric emptying) had an increased risk of gastric cancer following exposure to the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine. However, when combined with a drainage procedure such as pyloroplasty, thereby improving gastric emptying, risk of gastric cancer was decreased in vagotomised mice.[6]

Codeine and dihydrocodeine are widely prescribed opioid analgesics within the UK.[7] Both drugs are classed as weak opioids in the British National Formulary[8] and are used for mild to moderate pain on the World Health Organisation's analgesic ladder.[9] Opioids bind to mu receptors in the GI tract and decrease motility by inhibiting cholinergic neurotransmission,[10] and constipation is a well-documented side-effect in primary care.[11] Codeine has been shown in human studies to decrease oesophageal peristalsis,[12] delay gastric emptying,[13] and increase colonic transit time.[14]

To date, there has not been a study that has investigated the effect of weak opioids on risk of developing GI malignancy. Given their common usage and substantial effect on GI motility, we investigated the association between weak opioids and the risk of oesophageal, gastric, and colorectal cancer in a series of nested case-control studies within a large population-based general practice database.

2 Patients and Methods

2.1 Data Source

The study was conducted using data from the Primary Care Clinical Information Unit Research (PCCIUR) database.[15] The PCCIUR captures information from General Practice records including demographics, diagnoses, prescriptions, and lifestyle characteristics (including smoking and alcohol intake), and has been used extensively for research.[16–19] The PCCIUR contained over two million patients registered at 393 general practices in Scotland between 1993 and 2011. Data access was approved by the Research Applications and Data Management Team of the University of Aberdeen.

2.2 Study Design

A series of nested case-control studies were conducted within the PCCIUR database. New cases of oesophageal, gastric, and colorectal cancer, diagnosed between 1999 and 2011, were identified using General Practice Read codes. Cases were excluded if they had a diagnosis of another cancer, apart from non-melanoma skin cancer, on or before the date of their GI cancer diagnosis. Each case was matched with up to five controls based on gender, GP practice, year of birth plus-or-minus five years, and year of diagnosis (in categories). The date of cancer diagnosis was set as the index date for each case as well as their matched controls. Each control had to be alive and free from cancer, excluding non-melanoma skin cancer, and registered with their GP on the index date. Cases and controls were excluded if they did not have at least three years of continuous primary care records with the same general practice prior to the index date.

Within each matched set, the exposure period began on either 1st January 1993 (as the electronic prescription records are less likely to be complete before this time), or the most recent GP registration date within the matched set if this occurred after 1st January 1993. This method ensured that the exposure period was the same for cases and controls within each matched set. The exposure period finished one year before the index date to reduce the risk of reverse causation as medications taken during this period are unlikely to have contributed to carcinogenesis.

2.3 Exposure

We ascertained medication use from each individual prescription within the exposure period as classified in the British National Formulary.[8] We identified codeine prescriptions (including codeine alone and codeine with other medications; 96% of codeine prescriptions were a codeine and paracetamol compound medication) and dihydrocodeine prescriptions (including dihydrocodeine alone and dihydrocodeine combined with other medications; 62% of dihydrocodeine prescriptions were a dihydrocodeine and paracetamol compound medication). We also identified prescriptions for ibuprofen and paracetamol, commonly prescribed non-opioid analgesics, to act as active comparators.

2.4 Covariates

Relevant comorbidities were identified from published Read codes[20] to include in our analysis. We included the following comorbidities from the Charlson Comorbidity Index in all analyses: myocardial infarction, ischaemic heart disease, heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic pulmonary disease, peptic ulcer, rheumatological disease, HIV status and renal disease.

Additionally, inflammatory bowel disease was included in the model for colorectal cancer.[21] Medications which may have a preventative effect on GI tract cancer were incorporated into the model in all analyses, namely aspirin, statins, and non-steroidal anti-inflammatory drugs (NSAIDs),[22–25]. The Scottish Index of Multiple Deprivation based upon postcode of the GP practice was determined as a measure of deprivation.[26]

2.5 Statistical analyses

Characteristics of cases and controls were compared using frequencies and percentages for qualitative variables and descriptive statistics for continuous variables. We applied conditional logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI) for associations between weak opioids (either of codeine and/or dihydrocodeine), and oesophageal, gastric, and colorectal cancer. The matched design accounted for GP practice, sex, year of registration and age in categories, and, in addition, age in years was entered into both the unadjusted and adjusted models. We investigated use of weak opioids (including codeine or dihydrocodeine) and codeine and dihydrocodeine separately**.** We also investigated the number of prescriptions and timing of prescriptions (i.e. in the year immediately before cancer diagnosis, in the one-to-two year period before cancer diagnosis, two-to-three year period, and greater than three years prior).

We performed a number of further analyses. First, two active comparator analyses were conducted (to attempt to reduce confounding by indication)[27], one comparing weak opioid users to ibuprofen users (no adjustment was made for NSAIDs in this analysis), and another comparing weak opioid users to paracetamol users who had not used weak opioids. We performed an analysis additionally adjusting for smoking

and alcohol using a complete case approach and a multiple imputation approach. In the multiple imputation approach, smoking was imputed based upon an ordinal logistic regression model including case status and all covariates from the model including weak opioids. Twenty-five imputations[28] were conducted and results were combined using Rubin's rules.[29] This approach was used for smoking, alcohol, and both smoking and alcohol. We repeated the main analysis extending the lag period to 2 years to further reduce the risk of reverse causation. Finally, we conducted separate analyses of paracetamol prescriptions (i.e. excluding prescriptions containing weak opioids), and ibuprofen prescriptions to investigate pain medications, in general, on GI cancer risk. All statistical analyses were conducted using STATA 16 (StataCorp, College Station, TX, USA).

3 Results

3.1 Characteristics of cases and controls

Characteristics of cases and controls and selected comorbidities are summarised in Table 1. A total of 2,432 oesophageal, 1,443 gastric, and 8,750 colorectal cancer cases were matched with 10,590, 6,233, and 38,264 controls respectively. In all three cancer sites, most cases were diagnosed between the ages of 70-79 years old, and more cases were male. Smoking and alcohol consumption (where data was available) was similar between cases and controls.

3.2 Main analysis

3.2.1 Weak opioids and oesophageal cancer risk

We observed a small positive association between weak opioids and risk of oesophageal cancer (see Table 2, adjusted OR=1.16, CI 1.04, 1.29, p=0.01). This did not follow an obvious dose response as the association was apparent both in those with least use, 6 prescriptions or fewer, (adjusted OR=1.18, CI 1.05, 1.34, p=0.01) and those with highest use, more than 24 prescriptions (adjusted OR=1.26, CI 1.02, 1.56, p=0.04). Associations were similar for codeine and dihydrocodeine use (adjusted OR=1.12, CI 1.00, 1.25, p=0.05 and adjusted OR=1.06, CI 0.92, 1.23, p=0.43 respectively). The active comparator analysis showed there was no difference in oesophageal cancer risk in weak opioid users compared with ibuprofen users or paracetamol users. Further, the association between weak opioids and oesophageal cancer was only apparent in the first three years before diagnosis. Associations were largely similar in sensitivity analyses (see Table 4).

3.2.2 Weak opioids and gastric cancer risk

We observed a significant positive association between weak opioids and gastric cancer (see Table 2, adjusted OR=1.26, CI 1.10, 1.45, p=0.001). This appeared to follow an exposure response with individuals using more than 24 prescriptions having higher risk (adjusted OR=1.50, CI 1.18, 1.90, p=0.001). The associations were only apparent for codeine and not dihydrocodeine (adjusted OR 1.29, CI 1.12, 1.50, p=0.001 and adjusted OR=1.10, CI 0.92, 1.32, p=0.28 respectively). In the active comparator analysis, weak opioid users had a higher risk of gastric cancer compared with ibuprofen users (adjusted OR=1.29, CI 1.02, 1.64, p=0.04) but not paracetamol users. The association between weak opioids and gastric cancer was more marked in the year prior to cancer diagnosis but was still detectable more than

3 years before diagnosis (adjusted OR=1.21, CI 1.04, 1.41, p=0.01), when the lag period was extended to 2 years, and when adjusted for smoking and alcohol use (see Table 4). A separate analysis of paracetamol excluding weak opioid use (see Supplementary Table 1) showed a similar association with gastric cancer risk, with individuals receiving more than 24 prescriptions having a more marked increase in risk (adjusted OR=1.87, CI 1.32, 2.65, p<0.001).

3.2.3 Weak opioids and colorectal cancer risk

Table 3 shows there was no evidence of an association between weak opioids and colorectal cancer (adjusted OR=0.96, CI 0.90, 1.02, p=0.15). The findings were similar by frequency of use, by weak opioid type, and when active comparators were used. Findings were similar in sensitivity analyses (Table 4).

4 Discussion

In our study, we observed no consistent evidence of an association between weak opioids and oesophageal and colorectal cancer, but some evidence of association between weak opioids and gastric cancer. The gastric cancer risk appeared to follow an exposure response and remained when compared with ibuprofen, but was attenuated when compared to paracetamol and was similar to the association between paracetamol use and gastric cancer risk.

The cause of the association between weak opioids and gastric cancer is unknown. It could reflect our hypothesis that a decrease in GI motility increases risk of GI tract cancers. We chose to study weak opioids due to their well-documented side-effects of constipation[30] and their common usage in the UK.[7] There is also evidence of a direct effect of codeine on oesophageal peristalsis,[12] gastric emptying,[13] and colonic transit[14] in human studies. In support of this we observed an exposure response, and we observed an increased risk of gastric cancer in weak opioid users compared with ibuprofen users (who may share indications). Opioids have also been shown in experimental models to affect the integrity of GI epithelial cells[31] and increase pro-inflammatory cytokines through induction of the immune system.[32] Alternatively, the gastric cancer association could reflect confounding by indication and there was some evidence of this as the association between paracetamol, used for pain, and gastric cancer was similar to the association for weak opioids. Future studies of weak opioids and gastric cancer are warranted and should attempt to account for chronic pain.

The lack of association between weak opioids and oesophageal and colorectal cancer is reassuring to clinicians and patients. Weak opioids provide pain relief for mild to moderate pain in both acute and chronic settings and are included in the World Health Organisation's model list of essential medicines.[33]

Previous studies have provided some evidence for decreased GI motility and GI cancer risk. A 2019 study of a large Danish cohort by Sundbøll et al found patients with constipation had increased risk of oesophageal, stomach, small intestinal, liver, and pancreatic cancer at 15 years of follow-up; the authors posited that delayed motility may lead to dysbiosis of the GI flora, with toxic bacterial metabolites able to disseminate throughout the body.[1] Increased transit time may also be harmful by increasing exposure time of ingested or endogenously produced carcinogens to the GI mucosa; this has been suggested as a possible mechanism in the development of colorectal cancer,[34] however the evidence for constipation as a risk factor for colorectal cancer is conflicting.[2] Decreased GI motility has also been implicated in breast cancer, with the underlying mechanism thought to be decreased rate of oestrogen excretion from the increased GI transit time.[35] Conversely, exercise may decrease cancer risk by decreasing transit time and having a positive effect on gut microbiota composition.[3,36]

Our study has strengths and weaknesses. To our knowledge, this is the first study to focus upon weak opioids and GI cancer. The PCCIUR is population-based and captured prescription records for up to 18 years eliminating the potential for recall bias. PCCIUR primary care records have been shown to be largely accurate at

identifying cancer patients.[37] We adjusted for a wide range of potential confounders including smoking and alcohol which may be particularly important for GI cancer risk[38,39] but we did not have access to others such as body mass index and *Helicobacter pylori* status and hence there remains the possibility of residual confounding. We did not have cancer registry records to investigate GI cancer by histological subtype [4041]. We also did not have access to over-the-counter medication usage but codeine and dihydrocodeine are only available over the counter in the UK at low doses and with restricted pack sizes.[42,43] Further, methodological studies have shown that prescription data can give valid estimates of association even when medications are available over-the-counter.[44] It is possible that the observed association for weak opioids and gastric cancer could reflect Type I error. Finally, these results are not independent of an earlier screening study [16] using the PCCIUR database which observed in one analysis an association between codeine and gastric cancer, but that previous study did not investigate weak opioids, did not investigate the timing of medication use, or use active comparators to compare weak opioids with other pain medications.

5 Conclusion

We observed no consistent evidence of an association between weak opioids and an increased risk of oesophageal and colorectal cancer, but some evidence of a small association between weak opioids and gastric cancer. Opioids remain useful analgesics; further studies are required to replicate these findings, both for opioids and other medications which affect GI motility, to help inform clinicians' safe prescribing practice.

Ethics statement

We obtained ethics approval from the School of Medicine, Dentistry and Biomedical Sciences Research Ethics Committee at Queen's University Belfast (reference number: 18.02v2).

References

1. Sundbøll J, Thygesen SK, Veres K, Liao D, Zhao J, Gregersen H, et al. Risk of cancer in patients with constipation. Clin Epidemiol. 2019;11:299–310.

2. Power AM, Talley NJ, Ford AC. Association between constipation and colorectal cancer: Systematic review and meta-analysis of observational studies. Am J Gastroenterol. 2013;108(6):894–903.

3. Monda V, Villano I, Messina A, Valenzano A, Esposito T, Moscatelli F, et al. Exercise Modifies the Gut Microbiota with Positive Health Effects. Oxid Med Cell Longev. 2017;2017:3831972.

4. Akbarali HI, Dewey WL. Gastrointestinal motility, dysbiosis and opioid-induced tolerance: is there a link? Nat Rev Gastroenterol Hepatol. 2019;16(6):323–4.

5. Lam SY, Yu J, Wong SH, Peppelenbosch MP, Fuhler GM. The gastrointestinal microbiota and its role in oncogenesis. Best Pract Res Clin Gastroenterol. 2017;31(6):607–18.

6. Rabben H-L, Zhao C-M, Hayakawa Y, C. Wang T, Chen D. Vagotomy and Gastric Tumorigenesis. Curr Neuropharmacol. 2016;14(8):967–72.

7. Evidence Based Medicine DataLab University of Oxford. OpenPrescribing. [Internet]. Available from: https://openprescribing.net/chemical/0309010C0/ Accessed February 2022.

8. Joint Formulary Committee. British National Formulary. 83rd ed. London: BMJ Group and Pharmaceutical Press; 2022.

9. World Health Organization. WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. [Internet]. 2019. Available from: https://www.who.int/publications/i/item/9789241550390 . Accessed February 2022.

10. Sternini C, Patierno S, Selmer IS, Kirchgessner A. The opioid system in the gastrointestinal tract. Neurogastroenterol Motil. 2004;16(S2):3–16.

11. Shafe ACE, Lee S, Dalrymple JSO, Whorwell PJ. The LUCK study: Laxative Usage in patients with GP-diagnosed Constipation in the UK, within the general population and in pregnancy. An epidemiological study using the General Practice Research Database (GPRD). Therap Adv Gastroenterol. 2011;4(6):343.

12. Chen CL, Wong MW, Hung JS, Liang SW, Liu TT, Yi CH, et al. Effects of codeine on esophageal peristalsis in humans using high resolution manometry. J Gastroenterol Hepatol. 2021;36(12):3381–6.

13. Goelen N, de Hoon J, Morales JF, Varon C, Van Huffel S, Augustijns P, et al. Codeine delays gastric emptying through inhibition of gastric motility as assessed with a novel diagnostic intragastric balloon catheter. Neurogastroenterol Motil. 2020;32(1):e13733.

14. Mark EB, Klinge MW, Grønlund D, Poulsen JL, Schlageter V, Scott SM, et al. Ambulatory assessment of colonic motility using the electromagnetic capsule tracking system: Effect of opioids. Neurogastroenterol Motil. 2020;32(3):13753.

15. University of Aberdeen. Primary Care Clinical Informatics Unit Research. [Internet]. Available from: https://www.abdn.ac.uk/iahs/research/primary-care/pcciur/index.php . Accessed March 2022.

16. McDowell RD, Hughes C, Murchie P, Cardwell C. A systematic assessment of the association between frequently prescribed medicines and the risk of common cancers: a series of nested case-control studies. BMC Med. 2021;19(1):1–16.

17. Tran KT, McMenamin C, Hicks B, Murchie P, Thrift AP, Coleman HG, et al. Proton pump inhibitor and histamine-2 receptor antagonist use and risk of liver cancer in two population-based studies. Aliment Pharmacol Ther. 2018 Jul 1;48(1):55–64.

18. Spence AD, Busby J, Murchie P, Kunzmann AT, McMenamin ÚC, Coleman HG, et al. Medications that relax the lower oesophageal sphincter and risk of oesophageal cancer: An analysis of two independent population-based databases. Int J Cancer. 2018;143(1):22–31.

19. Macfarlane T V., Murchie P, Watson MC. Aspirin and other non-steroidal anti-inflammatory drug prescriptions and survival after the diagnosis of head and neck and oesophageal cancer. Cancer Epidemiol. 2015;39(6):1015–22.

20. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. BMC Fam Pract. 2010;11:1.

21. Stidham RW, Higgins PDR. Colorectal Cancer in Inflammatory Bowel Disease. Clin Colon Rectal Surg. 2018;31(3):168–78.

22. Jankowski JAZ, de Caestecker J, Love SB, Reilly G, Watson P, Sanders S, et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. Lancet. 2018;392(10145):400–8.

23. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet. 2007;369(9573):1603–13.

24. Friis S, Riis AH, Erichsen R, Baron JA, Sørensen HT. Low-dose aspirin or nonsteroidal anti-inflammatory drug use and colorectal cancer risk: A population-based, case-control study. Ann Intern Med. 2015;163(5):347–55.

25. Barbalata CI, Tefas LR, Achim M, Tomuta I, Porfire AS. Statins in risk-reduction and treatment of cancer. World J Clin Oncol. 2020;11(8):573–88.

26. Gov.scot. Scottish Index of Multiple Deprivation. [Internet]. 2020. Available from: https://www.gov.scot/publications/scottish-index-multiple-deprivation-2020/ . Accessed February 2022.

27. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. Nat Rev Rheumatol. 2015;11(7):437–41.

28. Graham JW, Olchowski AE, Gilreath TD. How Many Imputations are Really Needed? Some Practical Clarifications of Multiple Imputation Theory. Prev Sci. 2007;8(3):206–13.

29. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research:

Potential and pitfalls. BMJ. 2009;339(7713):157–60.

30. Wockhardt UK Ltd. Codeine Phosphate Tablets 30mg SmPC. [Internet]. Electronic Medicines Compendium. 2020. Available from: www.medicines.org.uk/emc/medicine/23916/SPC%5Cnpapers3://publication/uuid/EC85ED93-1AD6-4043-A19A-17842A4DB13A . Accessed February 2022.

31. Bauman BD, Meng J, Zhang L, Louiselle A, Zheng E, Banerjee S, et al. Enteric glial–mediated enhancement of intestinal barrier integrity is compromised by morphine. J Surg Res. 2017;219:214–21.

32. Palm S, Lehzen S, Mignat C, Steinmann J, Leimenstoll G, Maier C. Does prolonged oral treatment with sustained-release morphine tablets influence immune function? Anesth Analg. 1998;86(1):166–72.

33. World Health Organization. Model List of Essential Medicines. [Internet]. 2021. Available from: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02 . Accessed April 2022.

34. Burkitt D. Epidemiology of cancer of the colon and rectum. Dis Colon Rectum. 1977;1993(36):1071–82.

35. Maruti SS, Lampe JW, Potter JD, Ready A, White E. A prospective study of bowel motility and related factors on breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2008;17(7):1746–50.

36. Mctiernan A, Friedenreich CM, Katzmarzyk PT, Powell KE, Macko R, Buchner D, et al. Physical Activity in Cancer Prevention and Survival: A Systematic Review. Med Sci Sports Exerc. 2019;51(6):1252–61.

37. Margulis A V., Fortuny J, Kaye JA, Calingaert B, Reynolds M, Plana E, et al.

Validation of Cancer Cases Using Primary Care, Cancer Registry, and Hospitalization Data in the United Kingdom. Epidemiology. 2018;29(2):308–13.

38. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project: Diet, nutrition, physical activity and oesophageal cancer. [Internet]. 2018. Available from: https://www.wcrf.org/wp-content/uploads/2021/02/oesophageal-cancer-report.pdf . Accessed March 2022.

39. World Cancer Research Fund/American Institute for Cancer Research. Contiuous Update Project: Diet, nutrition, physical activity and stomach cancer. [Internet]. 2018. Available from: https://www.wcrf.org/sites/default/files/Stomach-cancer-report.pdf . Accessed March 2022.

40. Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, et al. Oesophageal cancer. Nat Rev Dis Prim. 2017;3(1):1–21.

41. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet. 2020;396(10251):635–48.

42. Foley M, Harris R, Rich E, Rapca A, Bergin M, Norman I, et al. The availability of over-the-counter codeine medicines across the European Union. Public Health. 2015;129(11):1465–70.

43. Medicines and Healthcare products Regulatory Agency. Codeine and dihydrocodeine-containing medicines: Minimising the risk of addiction. [Internet]. 2009. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/852388/Codeine_and_dihydrocodeine_minimising_the_ris

k_of_addiction.pdf . Accessed March 2022.

44. Yood MU, Campbell UB, Rothman KJ, Jick SS, Lang J, Wells KE, et al. Using prescription claims data for drugs available over-the-counter (OTC). Pharmacoepidemiol Drug Saf. 2007;16(9):961–8.

Table 1: Characteristics of cases and controls

Cancer site	Oesophageal		Gastric		Colorectal	
	Cases n=2,432	Controls n=10,590	Cases n=1,443	Controls n=6,233	Cases n=8,750	Controls n=38,264
Age; mean (SD)	69.1 (11.4)	66.5 (12.1)	71.2 (11.3)	68.9 (12.0)	69.6 (11.6)	67.2 (12.3)
<50	118 (4.9%)	869 (8.2%)	63 (4.4%)	401 (6.4%)	471 (5.4%)	3,132 (8.2%)
50-59	394 (16.2%)	2,322 (21.9%)	146 (10.1%)	915 (14.7%)	1,192 (13.6%)	7,005 (18.3%)
60-69	664 (27.3%)	2,923 (27.6%)	370 (25.6%)	1,712 (27.5%)	2,378 (27.2%)	10,887 (28.5%)
70-79	802 (33.0%)	2,825 (26.7%)	507 (35.1%)	1,989 (31.9%)	2,916 (33.3%)	10,850 (28.4%)
>80	454 (18.7%)	1,651 (15.6%)	357 (24.7%)	1,216 (19.5%)	1,793 (20.5%)	6,390 (16.7%)
Gender						
Male	1,645 (67.6%)	7,185 (67.8%)	827 (57.3%)	3,539 (56.8%)	4,795 (54.8%)	20,731 (54.2%)
Deprivation (in quintiles)						
1st (most deprived)	682 (28.0%)	2,950 (27.9%)	422 (29.2%)	1,820 (29.2%)	2,226 (25.4%)	9,637 (25.2%)
2nd	601 (24.7%)	2,619 (24.7%)	383 (26.5%)	1,648 (26.4%)	2,239 (25.6%)	9,761 (25.5%)
3rd	405 (16.7%)	1,791 (16.9%)	241 (16.7%)	1,055 (16.9%)	1,432 (16.4%)	6,307 (16.5%)
4th	483 (19.9%)	2,112 (19.9%)	263 (18.2%)	1,146 (18.4%)	1,840 (21.0%)	8,108 (21.2%)
5th (least deprived)	254 (10.4%)	1,087 (10.3%)	133 (9.2%)	559 (9.0%)	1,003 (11.5%)	4,410 (11.5%)
Missing	7 (0.3%)	31 (0.3%)	1 (0.1%)	5 (0.1%)	10 (0.1%)	41 (0.1%)
Smoking						
Never	633 (26.0%)	3,623 (34.2%)	476 (33.0%)	2,217 (35.6%)	3,120 (35.7%)	13,371 (34.9%)
Former	539 (22.2%)	2,079 (19.6%)	308 (21.3%)	1,246 (20.0%)	1,959 (22.4%)	7,297 (19.1%)
Current	726 (29.9%)	2,336 (22.1%)	349 (24.2%)	1,398 (22.4%)	1,657 (18.9%)	8,143 (21.3%)
Missing	534 (22.0%)	2,552 (24.1%)	310 (21.5%)	1,372 (22.0%)	2,014 (23.0%)	9,453 (24.7%)
Alcohol						
None	365 (15.0%)	1,413 (13.3%)	280 (19.4%)	999 (16.0%)	1,330 (15.2%)	5,738 (15.0%)
Low	1,126 (46.3%)	5,090 (48.1%)	655 (45.4%)	2,966 (47.6%)	4,265 (48.7%)	17,974 (47.0%)
High	152 (6.3%)	452 (4.3%)	44 (3.0%)	214 (3.4%)	328 (3.7%)	1,292 (3.4%)
Missing	789 (32.4%)	3,635 (34.3%)	464 (32.2%)	2,054 (33.0%)	2,827 (32.3%)	13,260 (34.7%)
Selected comorbidities						
Reflux oesophagitis	242 (10.0%)	530 (5.0%)	90 (6.2%)	356 (5.7%)	482 (5.5%)	1,868 (4.9%)
Barrett's oesophagus	96 (3.9%)	60 (0.6%)	6 (0.4%)	48 (0.8%)	52 (0.6%)	214 (0.6%)
Peptic ulcer disease	327 (13.4%)	917 (8.7%)	252 (17.5%)	630 (10.1%)	839 (9.6%)	3,205 (8.4%)
Diabetes mellitus	237 (9.7%)	900 (8.5%)	165 (11.4%)	537 (8.6%)	975 (11.1%)	3,122 (8.2%)
Myocardial infarction	193 (7.9%)	764 (7.2%)	129 (8.9%)	493 (7.9%)	603 (6.9%)	2,509 (6.6%)
IHD	455 (18.7%)	1,695 (16.0%)	329 (22.8%)	1,154 (18.5%)	1,514 (17.3%)	6,048 (15.8%)
Heart failure	109 (4.5%)	373 (3.5%)	64 (4.4%)	264 (4.2%)	350 (4.0%)	1,289 (3.4%)
PAD	159 (6.5%)	468 (4.4%)	90 (6.2%)	311 (5.0%)	425 (4.9%)	1,665 (4.4%)
IBD	141 (5.8%)	536 (5.1%)	85 (5.9%)	326 (5.2%)	502 (5.7%)	2,027 (5.3%)
Selected medications						
Aspirin	739 (30.4%)	2,904 (27.4%)	526 (36.5%)	1,919 (30.8%)	2,613 (29.9%)	10,447 (27.3%)
Statins†	573 (23.6%)	2,182 (20.6%)	345 (23.9%)	1,348 (21.6%)	1,956 (22.4%)	7,529 (19.7%)
NSAIDs‡	1,001 (41.2%)	4,416 (41.7%)	600 (41.6%)	2,658 (42.6%)	3,525 (40.3%)	15,753 (41.2%)

†Atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin.

‡Aceclofenac, acemetacin, celecoxib, dexibuprofen, dexketoprofen, diclofenac, etodolac, etoricoxib, fenoprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid, rofecoxib, valdecoxib, lumiracoxib.

Table 2: Exposure to weak opioids (codeine and dihydrocodeine) and risk of oesophageal and gastric cancer.

Medication	Cases	Controls	Age adjusted OR, 95% CI	Adjusted† OR, 95% CI	Adjusted† p value
Oesophageal cancer					
Weak opioids					
Non-user	1,563 (64.3%)	7,217 (68.1%)	1.00 (ref. category)	1.00 (ref. category)	
User	869 (35.7%)	3,373 (31.9%)	1.18 (1.06, 1.31)	1.16 (1.04, 1.29)	0.01
1-6 prescriptions	548 (22.5%)	2,123 (20.0%)	1.19 (1.06, 1.35)	1.18 (1.05, 1.34)	0.01
7-24 prescriptions	170 (7.0%)	729 (6.9%)	1.04 (0.87, 1.25)	1.02 (0.84, 1.23)	0.87
>24 prescriptions	151 (6.2%)	521 (4.9%)	1.34 (1.09, 1.65)	1.26 (1.02, 1.56)	0.04
Weak opioid type (user versus non-user)					
Codeine	700 (28.8%)	2,723 (25.7%)	1.14 (1.02, 1.27)	1.12 (1.00, 1.25)	0.05
Dihydrocodeine	334 (13.7%)	1,336 (12.6%)	1.11 (0.97, 1.28)	1.06 (0.92, 1.23)	0.43
Active comparator					
Ibuprofen users‡	215 (8.8%)	923 (8.7%)	1.00 (ref. category)	1.00 (ref. category)	
Weak opioid users	869 (35.7%)	3,373 (31.9%)	1.08 (0.91, 1.28)	1.03 (0.86, 1.22)	0.76
Paracetamol users‡	152 (6.3%)	615 (5.8%)	1.00 (ref. category)	1.00 (ref. category)	
Weak opioid users	869 (35.7%)	3,373 (31.9%)	1.22 (1.00, 1.50)	1.21 (0.99, 1.49)	0.07
Weak opioid use (by timing)					
0-1 years prior§	629 (25.9%)	1,868 (17.6%)	1.66 (1.49, 1.86)	1.63 (1.45, 1.83)	<0.001
1-2 years prior	475 (19.5%)	1,759 (16.6%)	1.19 (1.06, 1.35)	1.16 (1.02, 1.32)	0.02
2-3 years prior	435 (17.9%)	1,614 (15.2%)	1.20 (1.05, 1.36)	1.15 (1.01, 1.31)	0.03
>3 years prior¶	600 (26.3%)	2,390 (24.0%)	1.11 (0.99, 1.25)	1.08 (0.95, 1.22)	0.23
Gastric cancer					
Weak opioids					
Non-user	866 (60.0%)	4,087 (65.6)	1.00 (ref. category)	1.00 (ref. category)	
User	577 (40.0%)	2,146 (34.4%)	1.33 (1.17, 1.52)	1.26 (1.10, 1.45)	0.001
1-6 prescriptions	325 (22.5%)	1,291 (20.7%)	1.27 (1.09, 1.48)	1.22 (1.04, 1.43)	0.02
7-24 prescriptions	127 (8.8%)	463 (7.4%)	1.30 (1.04, 1.62)	1.20 (0.95, 1.52)	0.12
>24 prescriptions	125 (8.7%)	392 (6.3%)	1.59 (1.26, 2.01)	1.50 (1.18, 1.90)	0.001
Weak opioid type (user versus non-user)					
Codeine	476 (33.0%)	1,734 (27.8%)	1.36 (1.19, 1.57)	1.29 (1.12, 1.50)	0.001
Dihydrocodeine	226 (15.7%)	849 (13.6%)	1.18 (0.99, 1.40)	1.10 (0.92, 1.32)	0.28
Active comparator					
Ibuprofen users‡	109 (7.6%)	567 (9.1%)	1.00 (ref. category)	1.00 (ref. category)	
Weak opioid users	577 (40.0%)	2,146 (34.4%)	1.39 (1.10, 1.76)	1.29 (1.02, 1.64)	0.04
Paracetamol users‡	119 (8.2%)	429 (6.9%)	1.00 (ref. category)	1.00 (ref. category)	
Weak opioid users	577 (40.0%)	2,146 (34.4%)	1.13 (0.89, 1.43)	1.09 (0.86, 1.39)	0.45
Weak opioid use (by timing)					
0-1 years prior§	437 (30.3%)	1,247 (20.0%)	1.83 (1.59, 2.10)	1.76 (1.52, 2.03)	<0.001
1-2 years prior	341 (23.6%)	1,177 (18.9%)	1.34 (1.16, 1.55)	1.27 (1.09, 1.48)	0.002
2-3 years prior	306 (21.2%)	1,062 (17.0%)	1.30 (1.12, 1.52)	1.22 (1.04, 1.43)	0.02
>3 years prior¶	420 (30.8%)	1,557 (26.4%)	1.28 (1.11, 1.48)	1.21 (1.04, 1.41)	0.01

†Individually adjusted for comorbidities in the Charlson Comorbidity Index; peptic ulcer disease, diabetes, myocardial infarction, heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, liver disease, renal disease, HIV/AIDS, and aspirin, statin, and non-steroidal anti-inflammatory drug use (latter excluded in weak opioids/ibuprofen comparison).
‡Excludes weak opioid users.
§This time period is excluded from the main analysis.
¶Cases and controls excluded if less than four years of continuous records prior to index date:
Oesophageal cancer cases=2,285, controls=9,961
Gastric cancer cases=1,363, controls=5,891.

Table 3: Exposure to weak opioids (codeine and dihydrocodeine) and risk of colorectal cancer.

Medication	Cases	Controls	Age adjusted OR, 95% CI	Adjusted† OR, 95% CI	Adjusted† p value
			Colorectal cancer		
Weak opioids					
Non-user	5,977 (68.3%)	26,147 (68.3%)	1.00 (ref. category)	1.00 (ref. category)	
User	2,773 (31.7%)	12,117 (31.7%)	0.97 (0.92, 1.02)	0.96 (0.90, 1.02)	0.15
1-6 prescriptions	1,754 (20.0%)	7,458 (19.5%)	1.02 (0.95, 1.08)	1.01 (0.94, 1.07)	0.87
7-24 prescriptions	560 (6.4%)	2,648 (6.9%)	0.86 (0.78, 0.95)	0.85 (0.76, 0.94)	0.002
>24 prescriptions	459 (5.2%)	2,011 (5.3%)	0.93 (0.83, 1.04)	0.90 (0.80, 1.01)	0.08
Weak opioid type (user versus non-user)					
Codeine	2,271 (26.0%)	9,874 (25.8%)	0.97 (0.91, 1.03)	0.96 (0.90, 1.02)	0.20
Dihydrocodeine	1,052 (12.0%)	4,749 (12.4%)	0.95 (0.88, 1.03)	0.94 (0.87, 1.02)	0.16
Active comparator					
Ibuprofen users‡	788 (9.0%)	3,283 (8.6%)	1.00 (ref. category)	1.00 (ref. category)	
Weak opioid users	2,773 (31.7%)	12,117 (31.7%)	0.93 (0.84, 1.01)	0.91 (0.83, 1.00)	0.05
Paracetamol users‡	616 (7.0%)	2,282 (6.0%)	1.00 (ref. category)	1.00 (ref. category)	
Weak opioid users	2,773 (31.7%)	12,117 (31.7&)	0.94 (0.85, 1.04)	0.92 (0.83, 1.02)	0.12
Weak opioid use (by timing)					
0-1 years prior§	2,084 (23.8%)	7,051 (18.4%)	1.39 (1.31, 1.48)	1.40 (1.31, 1.49)	<0.001
1-2 years prior	1,516 (17.3%)	6,396 (16.7%)	1.01 (0.95, 1.08)	1.00 (0.93, 1.07)	0.97
2-3 years prior	1,356 (15.5%)	5,894 (15.4%)	0.97 (0.91, 1.04)	0.96 (0.90, 1.03)	0.30
>3 years prior¶	1,941 (23.8%)	8,700 (24.4%)	0.92 (0.87, 0.98)	0.91 (0.85, 0.97)	0.01

†Individually adjusted for comorbidities in the Charlson Comorbidity Index; peptic ulcer disease, diabetes, myocardial infarction, heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, liver disease, renal disease, HIV/AIDS, inflammatory bowel disease, and aspirin, statin, and non-steroidal anti-inflammatory drug use.
‡Excludes weak opioid users.
§This time period is excluded from the main analysis.
¶Cases and controls excluded if less than four years of continuous records prior to index date:
Colorectal cancer cases=8,162, controls=35,726

Table 4: Sensitivity analyses, weak opioids and gastrointestinal cancer risk.

Medication exposure	Cases	Controls	Adjusted† odds ratio, 95% confidence limits	Adjusted† p value
Oesophageal cancer				
Weak opioids (primary analysis)	2,432	10,590	1.16 (1.04, 1.29)	0.01
Weak opioids (2 year lag period)	2,285	9,961	1.12 (1.00, 1.26)	0.04
Additionally adjusted for smoking using complete case	1,898	8,038	1.15 (1.01, 1.30)	0.03
Additionally adjusted for smoking using multiple imputation	2,432	10,590	1.14 (1.02, 1.27)	0.03
Additionally adjusted for alcohol using multiple imputation	2,432	10,590	1.15 (1.03, 1.29)	0.01
Adjusting for smoking and alcohol using multiple imputation	2,432	10,590	1.13 (1.01, 1.26)	0.03
Gastric cancer				
Weak opioids (primary analysis)	1,443	6,233	1.26 (1.10, 1.45)	0.001
Weak opioids (2 year lag period)	1,363	5,891	1.27 (1.10, 1.47)	0.001
Additionally adjusted for smoking using complete case	1,133	4,861	1.25 (1.07, 1.47)	0.01
Additionally adjusted for smoking using multiple imputation	1,443	6,233	1.25 (1.09, 1.44)	0.002
Additionally adjusted for alcohol using multiple imputation	1,443	6,233	1.25 (1.09, 1.44)	0.002
Adjusting for smoking and alcohol using multiple imputation	1,443	6,233	1.24 (1.08, 1.43)	0.003
Colorectal cancer				
Weak opioids (primary analysis)	8,750	38,264	0.96 (0.90, 1.02)	0.15
Weak opioids (2 year lag period)	8,162	35,726	0.96 (0.90, 1.01)	0.14
Additionally adjusted for smoking using complete case	6,736	28,811	0.94 (0.88, 1.00)	0.06
Additionally adjusted for smoking using multiple imputation	8,750	38,264	0.96 (0.90, 1.02)	0.18
Additionally adjusted for alcohol using multiple imputation	8,750	38,264	0.96 (0.90, 1.02)	0.17
Adjusting for smoking and alcohol using multiple imputation	8,750	38,264	0.96 (0.91, 1.03)	0.22

†Individually adjusted for comorbidities in the Charlson Comorbidity Index; peptic ulcer disease, diabetes, myocardial infarction, heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, liver disease, renal disease, HIV/AIDS, and aspirin, statin, and non-steroidal anti-inflammatory drug use. Inflammatory bowel disease was also included in the model for colorectal cancer.

Supplementary Table 1: Exposure to paracetamol (not combined with weak opioids) and risk of gastrointestinal cancer.

Medication	Cases	Controls	Age-adjusted OR, 95% confidence limits	Adjusted† OR 95% confidence limits	Adjusted† p value
			Oesophageal cancer		
Non-user	2,039 (83.8%)	9,049 (85.4%)	1.00 (ref. category)	1.00 (ref. cat.)	
Paracetamol‡	393 (16.2%)	1,541 (14.6%)	0.99 (0.86, 1.13)	0.95 (0.83, 1.10)	0.50
1-6 prescriptions	249 (10.2%)	992 (9.4%)	0.98 (0.84, 1.15)	0.96 (0.82, 1.13)	0.63
7-24 prescriptions	97 (4.0%)	366 (3.5%)	0.99 (0.78, 1.27)	0.94 (0.73, 1.20)	0.62
>24 prescriptions	47 (1.9%)	183 (1.7%)	1.00 (0.71, 1.41)	0.94 (0.66, 1.34)	0.74
			Gastric cancer		
Non-user	1,132 (78.4%)	5,168 (82.9%)	1.00 (ref. category)	1.00 (ref. cat.)	
Paracetamol‡	311 (21.6%)	1,065 (17.1%)	1.22 (1.04, 1.43)	1.17 (1.00, 1.38)	0.05
1-6 prescriptions	172 (11.9%)	665 (10.7%)	1.11 (0.92, 1.35)	1.07 (0.88, 1.30)	0.52
7-24 prescriptions	85 (5.9%)	273 (4.4%)	1.20 (0.92, 1.57)	1.14 (0.87, 1.50)	0.34
>24 prescriptions	54 (3.7%)	127 (2.0%)	1.86 (1.33, 2.62)	1.87 (1.32, 2.65)	<0.001
			Colorectal cancer		
Non-user	7,346 (84.0%)	32,536 (85.0%)	1.00 (ref. category)	1.00 (ref. cat.)	
Paracetamol‡	1,404 (16.0%)	5,728 (15.0%)	0.95 (0.89, 1.02)	0.95 (0.88, 1.02)	0.18
1-6 prescriptions	879 (10.0%)	3,677 (19.6%)	0.94 (0.87, 1.02)	0.95 (0.87, 1.03)	0.20
7-24 prescriptions	373 (4.3%)	1,409 (3.7%)	0.99 (0.87, 1.12)	0.99 (0.88, 1.13)	0.92
>24 prescriptions	152 (1.7%)	642 (1.7%)	0.91 (0.75, 1.10)	0.88 (0.73, 1.07)	0.20

†Individually adjusted for comorbidities in the Charlson Comorbidity Index; peptic ulcer disease, diabetes, myocardial infarction, heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, liver disease, renal disease, HIV/AIDS, and aspirin, statin, and non-steroidal anti-inflammatory drugs use. Inflammatory bowel disease was also included in the model for colorectal cancer.

‡Participants who had a paracetamol prescription which did not contain a weak opioid.

Supplementary Table 2: Exposure to ibuprofen and risk of gastrointestinal cancer.

Medication	Cases	Controls	Age-adjusted OR, 95% confidence limits	Adjusted† OR 95% confidence limits	Adjusted† p value
			Oesophageal cancer		
Non-user	1,931 (79.4%)	8,513 (80.4%)	1.00 (ref. category)	1.00 (ref. cat.)	
Ibuprofen	501 (20.6%)	2,077 (19.6%)	1.07 (0.95, 1.21)	1.07 (0.95, 1.20)	0.28
1-6 prescriptions	421 (17.3%)	1,685 (15.9%)	1.13 (1.00, 1.28)	1.12 (0.99, 1.27))	0.08
7-24 prescriptions	63 (2.6%)	296 (2.8%)	0.88 (0.66, 1.17)	0.89 (0.66, 1.19)	0.43
>24 prescriptions	17 (0.7%)	96 (0.9%)	0.72 (0.42, 1.23)	0.73 (0.42, 1.25)	0.25
			Gastric cancer		
Non-user	1,133 (78.5%)	4,955 (79.5%)	1.00 (ref. category)	1.00 (ref. cat.)	
Ibuprofen	310 (21.5%)	1,278 (20.5%)	1.13 (0.97, 1.32)	1.12 (0.96, 1.31)	0.14
1-6 prescriptions	239 (16.6%)	1,057 (17.0%)	1.08 (0.91, 1.27)	1.06 (0.90, 1.26)	0.48
7-24 prescriptions	55 (3.8%)	173 (2.8%)	1.37 (0.99, 1.89)	1.35 (0.97, 1.88)	0.07
>24 prescriptions	16 (1.1%)	48 (0.8%)	1.46 (0.80, 2.64)	1.49 (0.82, 2.71)	0.19
			Colorectal cancer		
Non-user	6,999 (80.0%)	30,752 (80.4%)	1.00 (ref. category)	1.00 (ref. cat.)	
Ibuprofen	1,751 (20.0%)	7,512 (19.6%)	1.04 (0.97, 1.10)	1.03 (0.97, 1.10)	0.35
1-6 prescriptions	1,437 (16.4%)	6,083 (15.9%)	1.07 (1.00, 1.15)	1.07 (1.00, 1.14)	0.07
7-24 prescriptions	240 (2.7%)	1,107 (2.9%)	0.90 (0.77, 1.04)	0.88 (0.76, 1.02)	0.10
>24 prescriptions	74 (0.8%)	322 (0.8%)	0.91 (0.70, 1.19)	0.92 (0.71, 1.20)	0.54

†Individually adjusted for comorbidities in the Charlson Comorbidity Index; peptic ulcer disease, diabetes, myocardial infarction, heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, liver disease, renal disease, HIV/AIDS, and aspirin and statin use. Inflammatory bowel disease was also included in the model for colorectal cancer.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

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

Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure ☑
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ☑
		(*b*) Report category boundaries when continuous variables were categorized ☑
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ☑
Discussion		
Key results	18	Summarise key results with reference to study objectives ☑
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 ☑
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ☑
Generalisability	21	Discuss the generalisability (external validity) of the study results ☑
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 ☑

*Give information separately for cases and controls.

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.