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Research Article

Cancer Prevention Research

# No Decreased Risk of Gastrointestinal Cancers in Users of Metformin in The Netherlands; A Time-Varying Analysis of Metformin Exposure

Roy G. de Jong[1,2], Andrea M. Burden[3,4], Sander de Kort[2], Myrthe P. van Herk-Sukel[5], Pauline A. Vissers[6], Paddy K. Janssen[3,4,7,8], Harm R. Haak[9,10,11], Ad A. Masclee[12], Frank de Vries[3,4,11,13], and Maryska L. Janssen-Heijnen[14,15]

## Abstract

Previous studies on metformin use and gastrointestinal (GI) cancer risk have yielded inconclusive results on metformin's chemoprotective effects. We aimed to evaluate GI cancer risk in users of metformin in The Netherlands using a time-varying approach in a large population-based database. A cohort study was performed using the NCR-PHARMO database. Patients using ≥1 non-insulin antidiabetic drug (NIAD) during 1998 to 2011 were included ($N = 57{,}621$). Exposure to NIADs was modeled time-varyingly. Cox regression analysis estimated HRs of GI cancers in current metformin users versus current users of other NIADs. Covariables included age, sex, drugs known to impact cancer risk, history of hospitalization, and starting year of follow-up. A sensitivity analysis was performed, applying a new-user design. Current use of metformin was not associated with a decreased risk of GI cancer [HR, 0.97; 95% confidence interval (CI), 0.82–1.15] or specific GI cancer sites. The sensitivity analysis yielded comparable results. No decreasing trends were observed with increasing cumulative dose of metformin [HR 1.05, 95% CI, 0.85–1.28; HR 0.89, 95% CI, 0.73–1.10; HR 0.96, 95% CI, 0.77–1.19 for dose tertiles low (<405 g), medium (405–999 g), and high (≥999 g)]. In contrast, an increased risk of pancreatic cancer was found in current users of metformin plus insulin (HR, 4.90; 95% CI, 2.64–9.10). In conclusion, no decreased risk of GI cancer was found in current metformin users compared with current users of other NIADs. Variations in the exposure definition of metformin use may be one of the explanations of previously found reduced cancer risks in metformin users. *Cancer Prev Res; 10(5); 290–7. ©2017 AACR.*

## Introduction

Metformin is an antidiabetic drug (ADD) that is widely used as the preferred first-line treatment for hyperglycemia in type 2 diabetes mellitus (T2DM). The Dutch guideline for the treatment of T2DM advises metformin as first-line treatment as well, beside lifestyle advice such as dietary modification, physical exercise, and weight reduction (1).

Metformin not only effectively lowers the blood glucose concentration through inhibition of gluconeogenesis and glycogenolysis in the liver, but is also known to decrease insulin resistance and hyperinsulinemia through the insulin/IGF-1 signaling pathway (2, 3). Because insulin resistance is known to be a risk factor for cancer development, metformin may have a role in chemoprevention of cancer (4–6). Other ways through which metformin may reduce cancer risk are: (1) direct activation of AMP-activated protein kinase (AMPK) signaling, which leads to inhibition of the mTOR signaling pathway, and subsequently to reduced cell proliferation, protein synthesis, and tumor angiogenesis (4); (2) metformin may have anti-inflammatory effects on malignant cells and may inhibit malignant stem cells, which are important in cancer initiation, recurrence, and resistance to chemotherapies (7).

[1]Department of Internal Medicine, VieCuri Medical Centre, Venlo, the Netherlands. [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, GROW - School for Oncology and Developmental Biology, Maastricht University Medical Centre+, Maastricht, the Netherlands. [3]Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+, Maastricht, the Netherlands. [4]Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands. [5]PHARMO Institute for Drug Outcomes Research, Utrecht, the Netherlands. [6]Department of Research, Netherlands Comprehensive Cancer Organization, Utrecht, the Netherlands. [7]Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacology, Utrecht University, Utrecht, the Netherlands. [8]Department of Central Hospital Pharmacy, VieCuri Medical Centre, Venlo, the Netherlands. [9]Department of Internal Medicine, Máxima Medical Centre Eindhoven, Eindhoven, the Netherlands. [10]Division of General Internal Medicine, Department of Internal Medicine, Maastricht University Medical Centre+, Maastricht, the Netherlands. [11]Department of Health Services Research, CAPHRI School for Public Health and Primary Care, Maastricht University Medical Centre+, Maastricht, the Netherlands. [12]Division of Gastroenterology and Hepatology, Department of Internal Medicine, NUTRIM – School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, the Netherlands. [13]MRC Life-course Epidemiology Unit, University of Southampton, Southampton, United Kingdom. [14]Department of Epidemiology, GROW - School for Oncology and Developmental Biology, Maastricht University Medical Centre+, Maastricht, the Netherlands. [15]Department of Clinical Epidemiology, VieCuri Medical Centre, Venlo, the Netherlands.

**Note:** Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

**Corresponding Author:** Roy G. de Jong, Department of Internal Medicine, VieCuri Medical Centre, Tegelseweg 210, 5912 BL, Venlo, the Netherlands. Phone: +31 433 884 202; Fax: +31 433 875 093; E-mail: roy.dejong@maastrichtuniversity.nl

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Observational studies have shown reduced risks of up to 64% for colorectal cancer, 94% for liver cancer, and 85% for pancreatic cancer in patients with T2DM using metformin (8–15). However, the validity of the reported risk reductions in observational studies may be limited due to methodological issues, such as confounding by indication, prevalent user bias, and time-related biases (16–18). Moreover, recent studies that have used a time-varying approach of metformin exposure could not confirm the lower risk of several cancers with use of metformin (19, 20). Although metformin may contain antineoplastic properties based on the aforementioned *in vitro* evidence, this effect may not be clinically relevant and therefore not visible when applying an optimal exposure definition of metformin use in an observational design.

The aim of our study was to evaluate the risk of gastrointestinal (GI) cancers in patients with T2DM using metformin applying a time-varying approach to ADD exposure, and to show differences between a prevalent user design and a new-user design.

## Materials and Methods

### Data source

Data for this population-based cohort study were obtained from the PHARMO Database Network and linked at the individual patient level to the Eindhoven area of the Netherlands Cancer Registry (NCR). The construct and validity of the linked database have been described elsewhere (21). The Eindhoven area of the NCR, maintained by the Netherlands Comprehensive Cancer Organisation (NCCO), covers a demographic region with approximately 2.4 million inhabitants (~15% of the Dutch population). Trained registration clerks actively collect data on newly diagnosed cancers, patient characteristics, staging, and initial treatment from hospital medical records. Vital status is obtained by linkage to Dutch municipal records.

The PHARMO Database Network is a large, patient-centric data network including linked observational databases designed for drug safety and outcomes research. For this study, the Out-patient (community) Pharmacy Database was used, which contains longitudinal drug dispensing records, and included information on dispensing date, dose descriptions, and amount dispensed. All drugs are coded according to their Anatomical Therapeutic Chemical/Defined Daily Dose Classification (ATC/DDD) code (22). Both the NCR and the PHARMO Database Network are recognized as high-quality data sources for (pharmaco-)epidemiological research that have collected information in overlapping regions in the Netherlands for a period of over 10 years (21).

### Study design and population

We conducted a cohort study of all adult patients aged ≥30 years with at least one drug dispensing for an ADD [ATC codes "A10A" insulins, or "A10B" non-insulin antidiabetic drugs (NIAD)] in the NCR-PHARMO region between January 1, 1998, and December 31, 2011 (Fig. 1). The date of first recorded ADD defined the index date. We restricted the cohort to patients aged ≥30 years at the time of their first recorded prescription, as GI cancer rarely occurs before that age and to reduce misclassification by including type 1 diabetic patients. Patients for whom the first recorded ADD was insulin (ATC code "A10A") were excluded as they were more likely to have type 1 diabetes mellitus. Since coverage of the PHARMO database has gradually increased over time, there is a small chance that some prevalent T2DM patients were excluded, as patients could have entered the database at a later stage of their disease. Patients diagnosed with any type of GI cancer before the index date were excluded.

### Exposure classification

Follow-up time for all subjects was divided into fixed 90-day time intervals in order to model drug exposure over time in a time-varying way. Exposure to metformin and nonmetformin NIADs (other NIADs) was defined at the beginning of every 90-day interval. If a patient received a metformin or other NIAD prescription in the 90-days prior to the start of an interval, they were classified as a "current user" of that drug, otherwise they were classified as a "past user." All patients were classified as "current user" of either metformin or a nonmetformin other NIAD at each time interval, but they could move between current and past use throughout follow-up.

The cumulative dose of metformin was calculated at each current metformin use interval by summation of the total dose of each metformin prescription during the previous current use intervals. The whole sample median value was used to impute missing values of the recorded dose per tablet and for missing and/or extreme values of the amount of tablets dispensed. Cumulative dose at the end of follow-up was stratified by tertiles of cumulative metformin dose and classified as low (<405 g), medium (405–998 g), and high (≥999 g) cumulative dose.

### Outcomes

All patients were followed from the index date until a first ever diagnosis of a GI cancer, death from any cause, end of registration within the PHARMO catchment area, or end of data collection (December 31, 2011), whichever came first. GI cancers were classified according to the International Classification of Diseases of oncology (23). These included "any GI cancer" (C15-26), esophageal cancer (C15), gastric cancer (C16), small intestinal cancer (C17), colorectal cancer (CRC, C18-C20), hepatic cancer (C22), biliary tract cancer (C23: gallbladder, and C24: extrahepatic bile duct cancer), and pancreatic cancer (C25).

### Covariables

A number of covariables were considered as confounders based on the current literature. As time-fixed covariables sex and history of hospitalization prior to the index date (hospitalization categories 0 or ≥1) were considered. Time-dependent covariables were determined at the start of every 90-day time period and included age, the duration of diabetes in years (time since first recorded NIAD dispensing), and the use of other drugs known to impact GI cancer risk in the 90 days prior to the start of each interval [statins, aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAID), proton pump inhibitors, bisphosphonates, tamoxifen, oral contraceptives, and insulin). In addition, the use of helicobacter pylori (H. pylori) eradication therapy was used as proxy-indicator for H. pylori infection. Also, the year of start of follow-up was included as covariable as the index date of current metformin users and current users of other NIADs differed significantly at baseline (Table 1).

### Statistical analysis

Differences in demographic characteristics between current users of metformin and current users of other NIADs at baseline were compared using the Mann–Whitney *U* test for continuous variables and the $\chi^2$ test for categorical variables.

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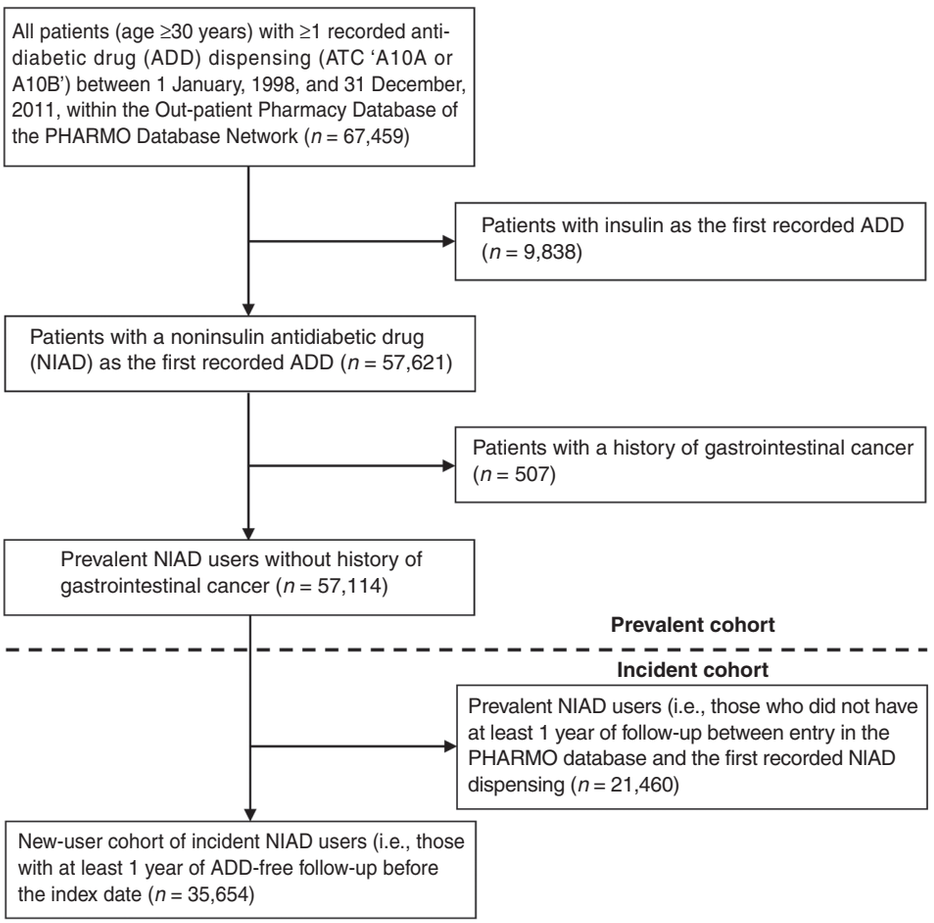


**Figure 1.**
Flow chart of study population.

Incidence rates per 100,000 person-years of follow-up were calculated by dividing the number of events by the total amount of person-years of follow-up. Overall and site-specific HRs and 95% confidence intervals (CI) of GI cancer in current users of metformin versus current users of other NIADs were calculated using time-varying Cox proportional hazards models. Stratified

**Table 1.** Baseline characteristics of current users of metformin or other NIADs

| | Current metformin users | | Current other NIADs users | | |
|---|---|---|---|---|---|
| **Characteristic** | ***n* = 37,215** | | ***n* = 19,899** | | ***P* value[a]** |
| Age (mean, SD) | 63.5 | 12.7 | 67.0 | 12.9 | <0.01 |
| Sex (*n*, % male) | 18,151 | 48.8 | 9,353 | 47.0 | <0.01 |
| Year of index date (mean, SD) | 2006 | 3.4 | 2002 | 3.4 | <0.01 |
| ADD use (*n*, %)[b] | | | | | |
| Metformin | 37,215 | 100.0 | 0 | 0.0 | <0.01 |
| SU | 4,621 | 12.4 | 19,166 | 96.3 | <0.01 |
| Thiazolidinediones | 357 | 1.0 | 632 | 3.2 | <0.01 |
| Meglitinides | 9 | 0.0 | 54 | 0.3 | <0.01 |
| Incretins | 71 | 0.2 | 53 | 0.3 | 0.06 |
| Use of other drugs (*n*, %)[c] | | | | | |
| Antihypertensives | 21,653 | 58.2 | 10,246 | 51.5 | <0.01 |
| Aspirin | 6,326 | 17.0 | 3,102 | 15.6 | <0.01 |
| Bisphosphonates | 922 | 2.5 | 549 | 2.8 | 0.04 |
| H. pylori eradication therapy | 41 | 0.1 | 9 | 0.1 | 0.01 |
| Non-aspirin NSAIDs | 4,832 | 13.0 | 2,630 | 13.2 | 0.43 |
| Proton pump inhibitors | 6,478 | 17.4 | 2,702 | 13.6 | <0.01 |
| Statins | 14,898 | 40.0 | 4,408 | 22.2 | <0.01 |
| History of hospitalization (*n*, %) | | | | | |
| 0 hospitalizations | 22,621 | 60.8 | 14,310 | 71.9 | |
| ≥1 hospitalizations | 14,594 | 39.2 | 5,589 | 28.1 | <0.01 |

[a]*P* value based on Mann–Whitney *U* test for continuous variables and $\chi^2$ test for categorical variables.
[b]At the start of follow-up (t0),
[c]During 90 days before the index date.

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**Table 2.** HRs of gastrointestinal cancer overall in current metformin users compared with current other NIAD users

| | Prevalent-user design | | | | New-user design | | | |
|---|---|---|---|---|---|---|---|---|
| **Exposure category** | **Events ($N = 1,076$)** | **IR** | **HR[a] (95% CI)** | **HR[b] (95% CI)** | **Events ($N = 612$)** | **IR** | **HR[a] (95% CI)** | **HR[b] (95% CI)** |
| Current other NIADs[c] | 214 | 457 | Ref. | Ref. | 120 | 556 | Ref. | Ref. |
| Current metformin | 624 | 376 | 0.96 (0.81–1.13) | 0.97 (0.82–1.15) | 361 | 391 | 0.91 (0.73–1.14) | 0.79 (0.59–1.06) |
| Stratified by treatment stage[d] | | | | | | | | |
| Metformin only | 277 | 341 | 0,83 (0.69–1.01) | 0.89 (0.73–1.07) | 208 | 359 | 0.81 (0.63–1.03) | 0.75 (0.55–1.04) |
| Metformin + SU | 269 | 432 | 1,07 (0.89–1.29) | 1.07 (0.89–1.29) | 117 | 450 | 1.06 (0.81–1.39) | 0.85 (0.60–1.21) |
| Metformin + other NIADs | 15 | 247 | 0,74 (0.43–1.26) | 0.75 (0.46–1.28) | 11 | 320 | 0.97 (0.52–1.82) | 0.79 (0.34–1.84) |
| Metformin + insulin | 63 | 379 | 1,15 (0.86–1.54) | 1.06 (0.78–1.43) | 25 | 496 | 1.57* (1.00–2.47) | 0.74 (0.36–1.51) |
| Stratified by cumulative dose[e] | | | | | | | | |
| Low | 201 | 376 | 0.93 (0.76–1.14) | 1.05 (0.85–1.28) | 143 | 429 | 0.95 (0.74–1.23) | 0.78 (0.54–1.11) |
| Medium | 196 | 343 | 0.88 (0.72–1.08) | 0.89 (0.73–1.10) | 109 | 324 | 0.76 (0.58–1.01) | 0.73 (0.51–1.04) |
| High | 227 | 408 | 1.10 (0.90–1.36) | 0.96 (0.77–1.19) | 109 | 430 | 1.10 (0.82–1.47) | 0.91 (0.62–1.34) |
| Past metformin | 194 | 361 | 0.95 (0.77–1.16) | 0.87 (0.70–1.07) | 115 | 397 | 0.95 (0.72–1.25) | 0.74 (0.52–1.06) |
| Past other NIADs | 44 | 281 | 0.66* (0.48–0.92) | 0.61* (0.44–0.84) | 16 | 199 | 0.41* (0.24–0.69) | 0.40* (0.21–0.76) |

Abbreviation: IR, incidence rate per 100,000 person-years.

[a]Age and sex adjusted.

[b]Adjusted for age, sex, use of statins, insulin, history of hospitalization, duration of diabetes, and year of start of follow-up.

[c]Excluding metformin.

[d]Fully adjusted model not adjusted for insulin use.

[e]Low: <405 g; Medium: 405–998 g; High: ≥999 g.

*Statistically significant with $P < 0.05$.

analyses were performed by sex, and by stratifying current metformin use by treatment stage and tertiles of cumulative dose. Subgroups of current metformin use by treatment stage included metformin monotherapy, metformin plus a sulfonylurea (SU) derivative, metformin plus another (non-SU) NIAD, and metformin plus insulin (regardless of other NIAD use). Potential confounders were entered into the regression models if they independently changed the β-coefficient for current metformin use by at least 5% in a univariate analysis.

### Sensitivity analyses

Sensitivity analyses with a new-user design were performed to account for prevalent user bias. The main analyses were repeated with an inception cohort of incident NIAD users only (Fig. 1). To create an inception cohort of incident NIAD users, we excluded all prevalent NIAD users, i.e., those who did not have at least 1 year of follow-up between entry in the PHARMO database and the first recorded NIAD dispensing. Data management and statistical analyses were conducted using SAS 9.4 software.

## Results

### Baseline characteristics

At the start of follow-up, 37,215 T2DM patients were current metformin users and 19,899 were current users of other NIADs (Table 1). Current metformin users were on average younger (mean age, 63.5 vs. 67.0 years, $P < 0.01$) and more often males (48.8% vs. 47.0%, $P < 0.01$) compared with current other NIAD users. The year of start of follow-up was more recent for current metformin users than current other NIAD users (mean, 2006 vs. 2002, $P < 0.01$). Most diabetic patients started follow-up either on metformin monotherapy or on SU (96.3% of current other NIAD users). Furthermore, current metformin users used more other drugs besides ADDs as compared with other NIAD users, such as statins (40.0% vs. 22.2%, $P < 0.01$), aspirin (17.0% vs. 15.6%, $P < 0.01$), anti-hypertensives (58.2% vs. 51.5%, $P < 0.01$), and proton pump inhibitors (17.4% vs. 13.6%, $P < 0.01$). Current metformin users were being hospitalized prior to the index date more often (39.2% vs. 28.1%, $P < 0.01$).

### GI cancer overall

During more than 280,000 person-years of follow-up (mean, 4.9 years per person), 1,076 GI cancers were observed (IR, 381 per 100,000 person-years). No statistically significant decreased risk of GI cancer was observed in current metformin users compared with current other NIAD users (fully adjusted HR 0.97; 95% CI, 0.82–1.15; Table 2). Stratified analyses of subgroups of current metformin use by treatment stage and tertiles of cumulative dose did not reveal a decreased risk of GI cancer. Furthermore, the sensitivity analysis and stratified analysis by sex yielded similar results (Table 2 and Supplementary Table S1, respectively).

### GI cancer sites

In the site-specific analyses, no significant differences in HRs of GI cancers were observed in current metformin users versus current other NIAD users (Table 3). However, a statistically significant increased HR of pancreatic cancer was observed in the subgroup of current users of metformin plus insulin (fully adjusted HR 4.90; 95% CI, 2.64–9.10) and in female current metformin users (fully adjusted HR 1.95; 95% CI, 1.01–3.76; Supplementary Table S2). Furthermore, there were no trends with increasing cumulative dose of metformin. In addition, the new-user design did not show statistically significant decreased HRs of GI cancer sites in current metformin users compared with current other NIAD users (Table 4), whereas increased HRs of pancreatic cancer with current use of metformin plus a SU derivative and metformin plus insulin remained (fully adjusted HR 1.98; 95% CI, 1.10–3.59 and fully adjusted HR 10.26; 95% CI, 4.96–21.22, respectively).

## Discussion

In this population-based cohort study, in which we used a time-varying approach to determine metformin exposure in diabetic patients, no reduced risk of GI cancer was found when comparing current use of metformin with current use of other NIADs. In

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**Table 3.** Site-specific HRs of GI cancer in current metformin users compared with current other NIAD users (prevalent cohort)

| Cancer site | Esophagus ($N = 84$) | | Stomach ($N = 108$) | | Liver ($N = 27$) | | Biliary tract ($N = 40$) | | Pancreas ($N = 175$) | | Colorectum ($N = 637$) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure category** | ***N*** | **HR[a] (95% CI)** | ***N*** | **HR[a] (95% CI)** | ***N*** | **HR[a] (95% CI)** | ***N*** | **HR[a] (95% CI)** | ***N*** | **HR[a] (95% CI)** | ***N*** | **HR[a] (95% CI)** |
| Current other NIADs[b] | 16 | Ref. | 22 | Ref. | <5 | Ref. | 9 | Ref. | 32 | Ref. | 132 | Ref. |
| Current metformin | 48 | 0.90 (0.48–1.67) | 61 | 1.06 (0.63–1.80) | 19 | 2.07 (0.58–7.43) | 20 | 1.36 (0.59–3.17) | 105 | 1.11 (0.72–1.71) | 368 | 0.89 (0.71–1.10) |
| Stratified by treatment stage[c] | | | | | | | | | | | | |
| Metformin only | 24 | 0.95 (0.48–1.87) | 20 | 0.74 (0.39–1.41) | 13 | 3.42 (0.92–12.76) | 10 | 1.61 (0.62–4.15) | 40 | 0.73 (0.44–1.12) | 165 | 0.86 (0.67–1.10) |
| Metformin + SU | 21 | 1.19 (0.61–2.34) | 35 | 1.42 (0.81–2.49) | 5 | 1.53 (0.36–6.59) | 10 | 1.99 (0.80–4.99) | 42 | 1.59 (0.98–2.57) | 158 | 0.93 (0.73–1.18) |
| Metformin + other NIADs | 0 | — | <5 | 1.14 (0.26–4.98) | 0 | — | 0 | — | <5 | 1.72 (0.59–4.96) | 9 | 0.68 (0.34–1.36) |
| Metformin + insulin | <5 | 0.69 (0.19–2.45) | <5 | 0.66 (0.22–2.00) | <5 | 1.35 (0.13–13.64) | 0 | — | 19 | 4.90* (2.64–9.10) | 36 | 0.83 (0.56–1.23) |
| Stratified by cumulative dose[d] | | | | | | | | | | | | |
| Low | 14 | 0.83 (0.40–1.75) | 20 | 1.29 (0.68–2.43) | 5 | 1.66 (0.39–7.14) | 8 | 1.44 (0.54–3.83) | 55 | 1.29 (0.81–2.07) | 97 | 0.86 (0.65–1.14) |
| Medium | 13 | 0.72 (0.33–1.57) | 18 | 0.94 (0.49–1.80) | 6 | 2.00 (0.47–8.50) | 6 | 1.18 (0.40–3.47) | 26 | 0.81 (0.47–1.42) | 123 | 0.89 (0.69–1.15) |
| High | 21 | 1.26 (0.60–2.65) | 23 | 0.96 (0.49–1.88) | 8 | 2.91 (0.69–12.24) | 6 | 1.49 (0.48–4.59) | 24 | 1.10 (0.58–2.06) | 148 | 0.91 (0.69–1.20) |
| Past metformin | 15 | 1.03 (0.48–2.20) | 20 | 0.96 (0.50–1.85) | <5 | 1.07 (0.21–5.54) | 11 | 2.00 (0.78–5.09) | 35 | 0.98 (0.58–1.67) | 110 | 0.77 (0.59–1.01) |
| Past other NIADs | 5 | 1.13 (0.41–3.12) | 5 | 0.68 (0.26–1.82) | <5 | 2.18 (0.36–13.16) | 0 | — | <5 | 0.26* (0.08–0.86) | 27 | 0.59* (0.39–0.89) |

[a]Adjusted for age, sex, use of statins (esophageal cancer, gastric cancer, biliary tract cancer, pancreatic cancer), proton pump inhibitors (esophageal cancer, gastric cancer), aspirin (gastric cancer, pancreatic cancer), antihypertensives (esophageal cancer, pancreatic cancer), helicobacter pylori eradication therapy (gastric cancer), insulin (esophageal cancer, gastric cancer, pancreatic cancer, colorectal cancer), history of hospitalization (esophageal cancer, gastric cancer, liver cancer, biliary tract cancer, pancreatic cancer, colorectal cancer), duration of diabetes (gastric cancer, pancreatic cancer, colorectal cancer), and year of start of follow-up (gastric cancer, pancreatic cancer, colorectal cancer).

[b]Excluding metformin.

[c]Not adjusted for insulin use.

[d]Low: <405 g; Medium: 405–998 g; High: ≥999 g.

*Statistically significant with $P < 0.05$.

**Table 4.** Site-specific HRs of GI cancer in current metformin users compared with current other NIAD users (new-user design)

| Cancer site | Esophagus ($N = 43$) | | Stomach ($N = 53$) | | Liver ($N = 15$) | | Biliary tract ($N = 20$) | | Pancreas ($N = 127$) | | Colorectum ($N = 352$) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure category** | ***N*** | **HR[a] (95% CI)** | ***N*** | **HR[a] (95% CI)** | ***N*** | **HR[a] (95% CI)** | ***N*** | **HR[a] (95% CI)** | ***N*** | **HR[a] (95% CI)** | ***N*** | **HR[a] (95% CI)** |
| Current other NIADs[b] | 6 | Ref. | 10 | Ref. | <5 | Ref. | <5 | Ref. | 23 | Ref. | 75 | Ref. |
| Current metformin | 29 | 1.59 (0.61–4.14) | 28 | 0.90 (0.41–1.97) | 11 | 1.44 (0.29–7.27) | 9 | 1.12 (0.32–3.94) | 79 | 1.14 (0.68–1.91) | 201 | 0.78 (0.58–1.05) |
| Stratified by treatment stage[c] | | | | | | | | | | | | |
| Metformin only | 20 | 2.07 (0.79–5.40) | 15 | 0.79 (0.33–1.88) | 7 | 1.93 (0.38–9.84) | 6 | 1.34 (0.36–5.00) | 35 | 0.71 (0.40–1.26) | 121 | 0.75 (0.54–1.03) |
| Metformin + SU | 9 | 2.18 (0.75–6.31) | 11 | 1.15 (0.47–2.84) | <5 | 2.37 (0.42–13.45) | <5 | 1.54 (0.33–7.09) | 26 | 1.98* (1.10–3.59) | 65 | 0.84 (0.59–1.19) |
| Metformin + other NIADs | 0 | — | <5 | 1.11 (0.14–8.95) | 0 | — | 0 | — | <5 | 2.74 (0.92–8.18) | 6 | 0.77 (0.33–1.80) |
| Metformin + insulin | 0 | — | <5 | 0.66 (0.08–5.47) | 0 | — | 0 | — | 14 | 10.26* (4.96–21.22) | 9 | 0.72 (0.35–1.48) |
| Stratified by cumulative dose[d] | | | | | | | | | | | | |
| Low | 9 | 1.35 (0.46–3.96) | 13 | 1.29 (0.53–3.13) | <5 | 0.80 (0.11–6.01) | <5 | 1.20 (0.29–4.98) | 46 | 1.23 (0.71–2.13) | 67 | 0.77 (0.54–1.10) |
| Medium | 7 | 1.16 (0.36–3.72) | 5 | 0.44 (0.15–1.35) | <5 | 1.60 (0.26–9.71) | <5 | 1.32 (0.31–5.70) | 19 | 0.88 (0.46–1.71) | 67 | 0.72 (0.50–1.02) |
| High | 13 | 3.32* (1.10–10.06) | 10 | 0.99 (0.36–2.72) | 5 | 2.75 (0.43–17.53) | <5 | 0.53 (0.05–5.24) | 14 | 1.34 (0.60–2.96) | 67 | 0.89 (0.61–1.31) |
| Past metformin | 7 | 1.46 (0.46–4.65) | 13 | 1.23 (0.50–3.01) | <5 | 0.43 (0.04–5.12) | 7 | 2.32 (0.63–8.60) | 24 | 0.94 (0.50–1.77) | 65 | 0.79 (0.55–1.13) |
| Past other NIADs | <5 | 0.64 (0.08–5.36) | <5 | 0.57 (0.12–2.63) | <5 | 1.42 (0.13–15.83) | 0 | — | <5 | 0.12* (0.02–0.90) | 11 | 0.41* (0.22–0.78) |

[a]Adjusted for age, sex, use of statins (esophageal cancer, gastric cancer, biliary tract cancer, pancreatic cancer), proton pump inhibitors (esophageal cancer, gastric cancer), aspirin (gastric cancer, pancreatic cancer), antihypertensives (esophageal cancer, pancreatic cancer), helicobacter pylori eradication therapy (gastric cancer), insulin (esophageal cancer, gastric cancer, pancreatic cancer, colorectal cancer), history of hospitalization (esophageal cancer, gastric cancer, liver cancer, biliary tract cancer, pancreatic cancer, colorectal cancer), duration of diabetes (gastric cancer, pancreatic cancer, colorectal cancer), and year of start of follow-up (gastric cancer, pancreatic cancer, colorectal cancer).

[b]Excluding metformin.

[c]Not adjusted for insulin use.

[d]Low: <405 g; Medium: 405–999 g; High: ≥999 g.

*Statistically significant with $P < 0.05$.

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addition, results from the sensitivity analysis, in which a new-user design was applied, did not significantly differ from the main analyses with a prevalent cohort of NIAD users. The risk of pancreatic cancer was increased in female current users of metformin, and in current users of metformin combined with insulin compared with current other NIAD users in both the main and sensitivity analysis.

The results of this study add to the evidence of recently published observational studies on the effect of metformin and (GI) cancer risk (20, 24–31). These studies showed no statistically significant reductions in GI cancer risk in users of metformin compared with users of other NIADs. Furthermore, these studies meet methodological standards due to a time-varying definition of exposure to metformin and because potential (time-related) biases have been adequately accounted for. The applied time-varying approach of metformin exposure in this study minimizes exposure misclassification and time-related bias. In addition, the results of our study will support future meta-analyses on the risk of GI cancer with use of metformin, and will help draw a firmer conclusion on metformin's chemoprotective effects.

The observed increased risk of pancreatic cancer in current users of metformin plus insulin and plus a SU derivative might be explained by the potential mitogenic effects of insulin and SU, as insulin secretagogues. A recent meta-analysis of observational studies reported an increased risk of pancreatic cancer with use of insulin versus NIADs (32). However, the authors advised cautious interpretation of their results as they had identified various methodological issues such as confounding by indication and time-related bias in multiple included studies (32). Bodmer and colleagues have reported an almost doubled risk of pancreatic cancer in users of SU (Adjusted OR 1.90; 95% CI, 1.32–2.74; ref. 10). However, also with respect to SU, studies on cancer risk have reported contrasting results (33). In addition, the increased risk of pancreatic cancer in these subgroups of current metformin use may be explained by protopathic bias. It is possible that SU or insulins were added to metformin treatment as a result of disturbances in glucose homeostasis by an emerging pancreatic cancer.

Meta-analyses of observational studies on metformin and cancer risk have presented mixed results for various GI cancers, possibly due to the high heterogeneity among included studies (e.g., in definition of T2DM, type of database, geographic region; refs. 33–40). Meta-analyses on metformin and cancer risk often combine results of observational studies with different types of exposure definitions to metformin, which potentially cause varying amounts of exposure misclassification and time-related bias. Future meta-analyses on the risk of cancer with use of metformin would benefit from an in-depth description of possible biases and confounding in all included studies, and by performing stratified analyses including only studies with a low level of confounding and bias. In fact, Gandini and colleagues performed a systematic review and meta-analysis of observational studies on metformin and cancer risk with emphasis on studies controlling for confounding by body mass index (BMI) and for time-related biases (41). Of the 47 included studies, only 18 were deemed to not have time-related biases. Regarding GI cancer risk, only the risk of colorectal cancer remained slightly decreased when analyzing studies without time-related bias [$N = 3$; summary relative risk (SRR), 0.92; 95% CI, 0.85–0.98]. Albeit, this decreased risk was not observed when analyzing studies that adjusted for BMI ($N = 6$). For liver and pancreatic cancer, no statistically significant decreased risks were found (SRR 0.77, 95% CI, 0.38–1.55 and 0.65, 95% CI, 0.39–1.08, respectively).

Certain limitations of our study merit discussion. First, it is possible that the results are not without any residual confounding due to our inability to correct for lifestyle factors (e.g., obesity, alcohol use, smoking status, and physical activity), diabetes severity (HbA1c), dietary habits, and the presence of unmeasured comorbidities (e.g., gastro-esophageal reflux disease, chronic liver disease, or chronic pancreatitis). Second, a lack of statistical power existed for some cancer sites, such as liver cancer, and biliary tract cancer, especially in the sensitivity analyses wherein a new-user cohort was used. This resulted in a limited ability to statistically adjust for confounders in the multivariate analyses. Third, confounding by indication could have influenced the results, which we tried to minimize by including a cohort of ADD users only. Metformin is prescribed more readily to obese diabetic patients, as it may contribute to weight loss. In turn, obesity and its proxy indicator, high BMI, are closely linked to GI cancer risk (42). Furthermore, although we compared metformin use with the use of other NIADs, the majority of other NIAD users was comprised of SU users with or without other NIADs (excluding metformin). Fourth, most GI cancers take decades to form, and the average follow-up time per person was 4.9 years. It is possible that the null results found in our study may be explained by the fact that most cancers were already present when patients started using metformin. Yet, we also do not know if metformin use may be able to slow down tumor progression, thereby delaying its diagnosis. Lastly, statistically significant inverse associations were found for GI cancer risk in past other NIAD users. The reasons, however, for becoming a past other NIAD user may vary greatly (e.g., start of insulin monotherapy or missing data due to a patient switching to a pharmacy outside the PHARMO catchment area). Therefore, the group of "past other NIAD use" is a very heterogeneous group, and no valid conclusions can be drawn from the point estimates in this group.

One of the major strengths of this study was the availability of complete and longitudinal drug dispensing data from PHARMO Database Network, which allowed us to model drug exposure during follow-up in a time-varying way. Furthermore, these drug dispensing data are derived directly from community pharmacies in the overlapping NCR-PHARMO region, with each dispensing being either picked up by the patient or directly delivered to the patient's address. Therefore, these data come very close to actual drug intake by the patient. In addition, cancer data from the NCR are known to contain high-quality data over a wide range of cancers and cancer characteristics, which guarantees a high level of cancer ascertainment. Furthermore, to account for prevalent user bias, we repeated the analyses in incident NIAD users. Inclusion of prevalent users in the main analyses could potentially introduce two biases. First, prevalent users probably have a survival benefit over incident users, as they are survivors of the early phase of therapy and make up a "survivor cohort" that generally consists of healthier patients. Secondly, prevalent drug use might alter the levels of risk factors (e.g., obesity, insulin resistance) over time, causing these risk factors to lose their confounding effect (17).

In summary, we found that in current metformin users, the risks of GI cancer were not significantly different from current other NIAD users. Our data add to the evidence of recent publications and highlight that methodological standards for drug exposure definitions should be met in observational studies. Future meta-

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analyses will benefit from an in-depth description of possible (time-related) biases and confounding factors in all included studies, and by performing stratified analyses by studies with a low level of confounding and bias.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** R.G. de Jong, A.A. Masclee, F. de Vries, M.L. Janssen-Heijnen

**Development of methodology:** R.G. de Jong, A.M. Burden, F. de Vries, M.L. Janssen-Heijnen

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** R.G. de Jong, M.P. van Herk-Sukel, P.A. Vissers, F. de Vries

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** R.G. de Jong, A.M. Burden, S. de Kort, P.A. Vissers, F. de Vries, M.L. Janssen-Heijnen

**Writing, review, and/or revision of the manuscript:** R.G. de Jong, A.M. Burden, S. de Kort, M.P. van Herk-Sukel, P.A. Vissers, P.K. Janssen, H.R. Haak, A.A. Masclee, F. de Vries, M.L. Janssen-Heijnen

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** R.G. de Jong

**Study supervision:** A.M. Burden, A.A. Masclee, F. de Vries, M.L. Janssen-Heijnen

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Cancer Prevention Research

# No Decreased Risk of Gastrointestinal Cancers in Users of Metformin in The Netherlands; A Time-Varying Analysis of Metformin Exposure

Roy G. de Jong, Andrea M. Burden, Sander de Kort, et al.

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