Metformin use and risk of gastric adenocarcinoma in a Swedish population-based cohort study

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BACKGROUND: Whether or not the use of metformin decreases the risk of gastric adenocarcinoma is unclear.

METHODS: This was a population-based cohort study in 2005–2015. Associations between metformin use and gastric non-cardia and cardia adenocarcinomas were examined within two cohorts; a diabetes cohort of participants using anti-diabetes medications, and a matched cohort of common-medication users, where metformin non-users were frequency matched (10:1) with metformin users for sex and age. Multivariable Cox proportional hazard regression analyses provided hazard ratios (HR) and 95% confidence intervals (CI), adjusting for sex, age, calendar year, comorbidity, Helicobacter pylori eradication treatment, use of non-steroidal anti-inflammatory drugs or aspirin and use of statins.

RESULTS: During the follow-up for a median of 5.8 years, 892 (0.1%) participants in the diabetes cohort and 6395 (0.1%) participants in the matched cohort of common-medication users developed gastric adenocarcinoma. Metformin users had no significantly decreased risk of gastric non-cardia adenocarcinoma (diabetes cohort: HR 0.93, 95% CI 0.78–1.12; matched cohort: HR 1.30, 95% CI 1.18–1.42) or cardia adenocarcinoma (diabetes cohort: HR 1.49, 95% CI 1.09–2.02; matched cohort: HR 1.58, 95% CI 1.38–1.81) compared with non-users in both cohorts.

CONCLUSIONS: This cohort study with <10 years of follow-up suggests metformin use may not prevent gastric adenocarcinoma.

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The Prescribed Drug Registry records individual-level data on all prescribed and dispensed drugs in Sweden since 1st July 2005. It covers 84% of the total drug sales in Sweden, the remaining part is medications sold over-the-counter or used in hospitals. Every year, ~66% of the Swedish population had at least one record in the Prescribed Drug Registry.

The Cancer Registry records data on all cancer diagnoses in Sweden from 1958 onwards. The completeness and positive predictive value of the diagnosis gastric adenocarcinoma are 98% and 96%, respectively.

The Patient Registry contains data on diagnoses and surgical and medical procedures in hospitals since 1987 and from specialist outpatient care since 2001. The positive predictive value of in-hospital diagnoses is in the range of 85–95%.

The Cause of Death Registry records causes and dates of death of all Swedish residents since 1952. The completeness of both date of death and causes of death data is at least 99%.

The linkages of individuals’ data between these registries were enabled by the 10-digit unique personal identity number assigned to each Swedish resident upon birth or immigration.

Study design
This was a population-based cohort study from 1st July 2005 to 31st December 2015. All individuals in SPREDH during this study period were potentially eligible for the study. The three exclusion criteria were: (1) previous cancer diagnosis (other than non-melanoma skin cancer) before the cohort entry (defined by the 7th edition of the International Classification of Diseases [ICD-7] codes 140–209, excluding 191 in the Cancer Registry); (2) gastrectomy conducted before the cohort entry (identified by the Nordic Medico-Statistical Committee Classification of Surgical Procedures codes 4411–4420, 4422, 4424–4426, 4429, 4430, 4432, 4434 and 4435 before 1997 and JDC and JDD from 1997 onwards in the Patient Registry); and (3) age below 18 years at the cohort entry.

Two study cohorts
Two cohorts were identified from the source cohort, a ‘diabetes cohort’ and a ‘matched cohort of common-medication users’.

The diabetes cohort. Individuals in SPREDH were included in the diabetes cohort based on their history of using anti-diabetic medications, defined by any dispensed record of anti-diabetic medication(s) (represented by the Anatomical Therapeutic Chemical [ATC] codes A10A and A10B in the Prescribed Drug Registry) during the study period. The exposed group was users of metformin, with or without other anti-diabetic medications, represented by the ATC codes A10BA02, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10BD20 and A10BD22 in the Prescribed Drug Registry. The unexposed group consisted of users of anti-diabetic medication(s) other than metformin, i.e., metformin non-users. The entry date into the diabetes cohort was the first dispensation date of any anti-diabetic medication. To exclude individuals using anti-diabetic medications for other indications than diabetes, we excluded women with diagnoses of gestational diabetes (represented by the Swedish ICD-10 codes O24.4 and O24.9) or polycystic ovarian syndrome (represented by the Swedish ICD-10 code E28.2) in the Patient Registry. However, if a woman with polycystic ovarian syndrome had a first dispensation record of anti-diabetic medication other than metformin, or a later dispensation record of a second anti-diabetic medication, she would be included at the first dispensation date of any anti-diabetic medication(s) other than metformin. In the latter case, the woman was regarded exposed at the cohort entry. The exposure status was allowed to change, i.e., an unexposed participant became exposed at the first purchase of metformin.

The matched cohort of common-medication users. This cohort was also derived from SPREDH. The exposed group was metformin users, defined by those who had any dispensing record of metformin in the Prescribed Drug Registry (details above). However, women with any diagnosis of gestational diabetes or polycystic ovarian syndrome were not excluded from the exposed group. The entry date of the metformin users was the first dispensation date of metformin. For each metformin user, ten non-users of metformin were randomly sampled from SPREDH as comparison participants, using frequency matching by age (± 1 year) and sex. Thus, the comparison participants entered the cohort on the same date as their matched metformin users. The exposure status was allowed to change also in this cohort.

Study outcomes
Newly diagnosed gastric adenocarcinomas during the study period were identified from the Cancer Registry by the ICD-7 code 151 combined with the histology code 096 for adenocarcinoma in the WHO/HS/CANC/24.1 classification. Gastric non-cardia adenocarcinoma (ICD-7 code 151, excluding 151.1, and histology code 096) and cardia adenocarcinoma (ICD-7 code 151.1 and histology code 096) were the outcomes. All cohort members were followed up until the occurrence of any gastric adenocarcinoma, death or the end of the study (December 31st, 2015), whichever occurred first.

Potential confounders
Seven factors were considered as potential confounders, for their possible associations with both metformin use and risk of gastric adenocarcinoma: (1) sex (male or female), (2) age (continuous), (3) calendar year (categorised as 2005, 2006–2010 or 2011–2015), (4) comorbidity (Charlson comorbidity index, categorised as 0, 1 or ≥ 2), (5) H. pylori eradication treatment (yes or no), (6) use of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin (yes or no) and (7) use of statins (yes or no).

Comorbidities (excluding diabetes) diagnosed within 10 years before the cohort entry were searched in the Patient Registry, and were handled using the well-validated Charlson comorbidity index. While no direct data on H. pylori infection were available, a dispensed record of standard H. pylori eradication packages (ATC code A02BD in the Prescribed Drug Registry) was used to represent clinically diagnosed H. pylori infection. These H. pylori eradication packages account for 85% of the H. pylori eradication therapy in Sweden.22 H. pylori eradication treatment was treated as a time-varying variable. Use of NSAIDs or aspirin23 and use of statins24 were also identified by the ATC codes in the Prescribed Drug Registry (for NSAIDs and aspirin: M01A, N02BA, B01AAC06, C10BX01, C10BX02, C10BX04, C10BX05, C10BX06, C10BX08, C10BX12, C07FX02, C07FX03 and C07FX04; for statins: C10AA and C10B) and were categorised as binary variables (yes or no). To be identified as a user of these medications, an individual had to have at least two dispensation records within the first year after cohort entry.

Statistical analysis
Multivariable Cox proportional hazards regressions were used to estimate the hazard ratios (HR) with 95% confidence intervals (CI) of gastric adenocarcinomas comparing metformin users with non-users in both the diabetes cohort and the matched cohort of common-medication users. The risks of gastric non-cardia and cardia adenocarcinomas were analysed combined and separately in both cohorts. Two models were applied, a crude model (without any adjustment) and a model with adjustment for the seven potential confounders presented and categorised above.

Six sub-group analyses were performed specifically for the risk of gastric non-cardia adenocarcinoma: (1) A dose–response analysis was examined among all users of metformin only. Metformin use was categorised into three levels according to the
total defined daily dose (DDD) in the first year after the first known date of dispensation: <175 DDDS, 175–300 DDDS and > 300 DDDS. P-value for trend was tested by treating the dose as a continuous variable based on the median values of each category. The remaining five sub-group analyses were performed only in the diabetes cohort; (2) stratified analyses by sex, age (above and below the median) and duration of follow-up (≤3 years, 3–6 years and ≥6 years); (3) sensitivity analyses, excluding individuals with less than 1 year of follow-up; (4) sensitivity analyses comparing non-users with prevalent users of metformin, with prevalent users being those who had at least one dispensation of metformin within the first year after the Prescribed Drug Registry came into use, i.e., between 2005 July 1st and 2006 June 30th; (5) sensitivity analyses restricted to participants with a history of H. pylori eradication therapy and lower overall mortality (Table 1). During the follow-up for a median of 5.8 years (interquartile range 2.3–10.0), 892 (0.1%) participants developed gastric adenocarcinoma.

Table 1. Characteristics of the study participants in the diabetes cohort and the matched cohort of common-medication users, numbers (%)

| Characteristic                   | Diabetes cohort |          | Matched cohort |          |
|----------------------------------|-----------------|---------|----------------|---------|
|                                 | Metformin users | Non-users | Metformin users | Non-users |
| **Total**                        | 334,506 (61.5)  | 209,624 | 411,413 (9.1)  | 4,114,130 (90.9) |
| **Sex**                          |                 |         |                |         |
| Men                              | 196,721 (58.8)  | 120,048 | 239,256 (58.2) | 2,392,560 (58.2) |
| Women                            | 137,785 (41.2)  | 89,576  | 172,157 (41.8) | 17,211,570 (41.8) |
| **Age at entry, mean ± standard deviation** | 62.1 (± 12.9) | 61.4 (± 19.5) | 59.0 (± 13.7) | 59.0 (± 13.7) |
| **Calendar year at entry**       |                 |         |                |         |
| 2005                             | 102,834 (30.7)  | 142,293 | 127,136 (30.9) | 1,271,360 (30.9) |
| 2006–2010                        | 111,199 (33.2)  | 41,432  | 146,175 (35.5) | 1,461,750 (35.5) |
| 2011–2015                        | 120,473 (36.0)  | 25,899  | 138,102 (33.6) | 1,381,020 (33.6) |
| **Charlson comorbidity**         |                 |         |                |         |
| 0                                | 250,635 (74.9)  | 135,583 | 303,840 (73.9) | 3,265,518 (79.4) |
| 1                                | 59,847 (17.9)   | 43,510  | 75,396 (18.3)  | 618,631 (15.0) |
| ≥2                               | 24,024 (7.2)    | 30,531  | 32,177 (7.8)   | 229,981 (5.6) |
| **Use of non-steroidal anti-inflammatory drugs or aspirin** |                 |         |                |         |
| No                               | 175,589 (52.5)  | 109,565 | 247,988 (60.3) | 3,048,169 (74.1) |
| Yes                              | 158,920 (47.5)  | 100,059 | 163,425 (39.7) | 1,065,961 (25.9) |
| **Use of statin**                |                 |         |                |         |
| No                               | 162,671 (48.6)  | 129,555 | 22,841 (54.2)  | 3,377,102 (82.1) |
| Yes                              | 171,835 (51.4)  | 80,069  | 188,572 (45.8) | 737,028 (17.9) |
| **Helicobacter pylori eradication** |                 |         |                |         |
| No                               | 324,885 (97.1)  | 205,024 | 399,781 (97.2) | 4,027,949 (97.9) |
| Yes, before entry                | 3515 (1.1)      | 762 (0.4) | 4238 (1.0)     | 33,813 (0.8) |
| Yes, after entry                 | 6106 (1.8)      | 3838 (1.8) | 7394 (1.8)     | 52,368 (1.3) |
| **Death during follow-up**       |                 |         |                |         |
| No                               | 282,110 (84.3)  | 133,819 | 340,543 (82.8) | 3,590,316 (87.3) |
| Yes                              | 52,396 (15.7)   | 75,805  | 70,870 (17.2)  | 523,814 (12.7) |

*aAt study entry
*bIn the 10 years before study entry
*cIn the year after study entry

RESULTS

Participants in the diabetes cohort
The diabetes cohort included 544,130 participants. At the cohort entry, 334,506 (61.5%) of these were metformin users, and 209,624 (38.5%) were non-users of metformin. A total of 72,643 (13.4%) non-users at baseline started using metformin during the follow-up. The number of person-years exposed to metformin was 2,432,273, and the number of person-years not exposed to metformin was 998,884. Compared with non-users, metformin users had less comorbidity, a higher proportion of users of statins, a higher proportion with H. pylori eradication therapy and lower overall mortality (Table 1). During the follow-up for a median of 5.8 years (interquartile range 2.3–10.0), 892 (0.1%) participants developed gastric adenocarcinoma.

Participants in the matched cohort of common-medication users
The matched cohort of common-medication users included 4,525,543 participants. Of these, 411,413 (9.1%) were metformin users and 4,114,130 (90.9%) were age-matched and sex-matched non-users of metformin. The number of person-years exposed to metformin was 2,457,824, and the number of person-years not exposed to metformin was 23,912,966. Compared with non-users, metformin users had more comorbidity, higher proportions of users of NSAIDs or aspirin and statins and higher overall mortality, whereas the proportion with H. pylori eradication therapy was similar in users and non-users.
of metformin (Table 1). During the follow-up for a median of 5.8 years (interquartile range 2.8–9.4 years), 6395 (0.1%) participants developed gastric adenocarcinoma.

Risk of total gastric adenocarcinoma
In the diabetes cohort, metformin use was not associated with any decreased risk of gastric adenocarcinoma (adjusted HR 1.08, 95% CI 0.92–1.26). Similarly, the results of the matched cohort of common-medication users revealed no decreased risk of total gastric adenocarcinoma in metformin users compared with non-users, but rather an increased risk (adjusted HR 1.30, 95% CI 1.18–1.50) (Table 2).

Risk of gastric non-cardia adenocarcinoma
In the diabetes cohort, use of metformin did not influence the risk of gastric non-cardia adenocarcinoma (adjusted HR 1.08, 95% CI 0.92–1.26). In the matched cohort of common-medication users, revealed no decreased risk of total gastric adenocarcinoma (Table 3). In the sub-group analyses, no dose–response relation for metformin use and the risk of non-cardia adenocarcinoma was found. Compared with participants who used a low dose (<175 DDD) of metformin, those who used a moderate dose (175–300 DDD) or a high dose (>300 DDD) did not have any reduced risk of gastric non-cardia adenocarcinoma (Table 3). In the stratified analyses of the diabetes cohort, metformin use was not associated with any decreased risk of gastric non-cardia adenocarcinoma in any of the sex or age groups, or in different durations of follow-up.

**DISCUSSION**

This study indicates that metformin use does not decrease the risk of gastric non-cardia or cardia adenocarcinoma in a Western population during the follow-up for a median of 6 years. Strengths of the study include the population-based cohort design, the use of high-quality data with nationwide coverage and the complete follow-up. This study is also the first to analyse gastric non-cardia and cardia adenocarcinomas separately. Several potential confounders were taken into account, including Helicobacter pylori infection and use of certain medications that may affect the risk of gastric adenocarcinoma. Yet, a limitation of the study was the lack of information on some other potential confounders, particularly obesity. Obesity is associated with an increased risk of gastric cardia adenocarcinoma, and diabetes patients are generally more obese than non-diabetic people.

Besides, diabetes patients using metformin have been reported to have even higher body mass index than diabetes patients treated by other medications. Thus, the increased risk estimates of gastric cardia adenocarcinoma among metformin users in this study might well be explained by confounding by obesity. However, confounding by obesity should not be a problem in the analyses of gastric non-cardia adenocarcinoma, because obesity is not a risk factor for gastric non-cardia adenocarcinoma. This was the rationale for conducting the post hoc sub-group analyses for gastric non-cardia adenocarcinoma only. Another limitation was the relatively short follow-up (maximum 10 years), because data on drug use before July 2005 (when the Prescribed Drug Registry started) were not available. It is possible that any protective effect of metformin is limited in the very early stage of gastric carcinogenesis, and therefore may be missed by the current study. Thus, the risks of gastric non-cardia and cardia adenocarcinoma in relation to the use of

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**Table 2.** Risk of total, non-cardia and cardia gastric adenocarcinomas in metformin users compared with non-users in the diabetes cohort and the matched cohort of common-medication users

|                         | Number of cases | Crude HR (95% CI) | Adjusted HR (95% CI)* |
|-------------------------|-----------------|-------------------|-----------------------|
| **Total adenocarcinoma**|                 |                   |                       |
| Diabetes cohort         |                 |                   |                       |
| Non-users               | 233             | Reference         | Reference             |
| Metformin users         | 659             | 0.99 (0.85–1.15)  | 1.08 (0.92–1.26)      |
| Matched cohort          |                 |                   |                       |
| Non-users               | 5606            | Reference         | Reference             |
| Metformin users         | 789             | 1.37 (1.26–1.48)  | 1.38 (1.26–1.50)      |
| **Non-cardia adenocarcinoma** |       |                   |                       |
| Diabetes cohort         |                 |                   |                       |
| Non-users               | 173             | Reference         | Reference             |
| Metformin users         | 421             | 0.88 (0.73–1.05)  | 0.93 (0.78–1.12)      |
| Matched cohort          |                 |                   |                       |
| Non-users               | 4061            | Reference         | Reference             |
| Metformin users         | 533             | 1.28 (1.16–1.41)  | 1.30 (1.18–1.42)      |
| **Cardia adenocarcinoma** |             |                   |                       |
| Diabetes cohort         |                 |                   |                       |
| Non-users               | 60              | Reference         | Reference             |
| Metformin users         | 238             | 1.30 (0.97–1.74)  | 1.49 (1.09–2.02)      |
| Matched cohort          |                 |                   |                       |
| Non-users               | 1545            | Reference         | Reference             |
| Metformin users         | 256             | 1.61 (1.39–1.86)  | 1.58 (1.38–1.81)      |

*HR hazard ratio, CI confidence interval
aAdjusted for sex, age, calendar year, use of non-steroidal anti-inflammatory drugs or aspirin, use of statins, Charlson comorbidity index and Helicobacter pylori eradication treatment

**Table 3.** Dose–response analysis for the risk of gastric non-cardia adenocarcinoma among metformin users

| Dosagea | Number of cases | Crude HR (95% CI) | Adjusted HR (95% CI)b |
|---------|-----------------|-------------------|-----------------------|
| Less than 175 DDD | 99 | Reference | Reference |
| 175–300 DDD    | 122 | 1.06 (0.81–1.39) | 1.01 (0.77–1.32) |
| More than 300 DDD | 147 | 0.99 (0.77–1.29) | 1.02 (0.77–1.34) |

P for trend [0.887, 0.904]
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indicated a decreased risk of gastric adenocarcinoma in metformin users, with HRs ranging from 0.83 to 0.45. 29,32,33,36 A recent cohort study from Hong Kong in diabetes patients who had received H. pylori eradication therapy found a reduced risk of gastric adenocarcinoma in metformin users (HR 0.49, 95% CI 0.24–0.98), 33 which was inconsistent with our results. This study adds to the limited body of literature in Western populations and the lack of any protective effect is supported by two other studies from Western populations, one from the United States and the other from Italy. 31,32

A novel aspect of this study was the analyses in the matched cohort of common-medication users, besides a diabetes cohort. While no association between metformin use and risk of gastric non-cardia adenocarcinoma was found in the diabetes cohort, it is interesting that an increased risk of gastric non-cardia adenocarcinoma was suggested among metformin users compared with non-users in this matched cohort. This difference indicates a role of diabetes or diabetes-related factors in the aetiology of gastric adenocarcinoma, which highlight a need for research on this topic. However, the existing literature has provided inconclusive evidence regarding the effects of diabetes on the risks of gastric adenocarcinoma and gastric cardia adenocarcinoma. 32,42

In conclusion, this large and population-based cohort study in Sweden does not support the hypothesis that use of metformin decreases the risk of gastric non-cardia or cardia adenocarcinoma within the initial years of follow-up.

**AUTHOR CONTRIBUTIONS**

All authors designed the study. J.L. and S.X. collected the data for the study. G.S. analysed the data. J.Z. interpreted the results and drafted the paper. All listed authors revised the paper and approved the final version of the article, including the authorship list. J.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**ADDITIONAL INFORMATION**

**Competing interests:** The authors declare no competing interests.

**Ethics approval and consent to participate:** The study was conducted conforming to the Declaration of Helsinki. According to the Swedish legislation (1998:543) on health data registries, informed consents were generally not needed for registry-based studies in Sweden if the studies had been approved by the local ethical board. 41 This study was approved by Regional Ethical Review Board in Stockholm, Sweden (reference number 2016/982-3/4).

**Consent for publication:** Not applicable

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Data availability: All the data in this study were retrieved from the Swedish Prescribed Drugs and Health Cohort. The original data are available from the related registries listed above but restrictions apply to the availability of these data, which were used under license for this study and therefore are not publicly available. The data are, however, available through applications to these registries or reasonable request to the corresponding author (S.X.). The codes for the data analysis are archived by the biostatistician (G.S.).

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**Table 4. Sub-group analyses of the risk of gastric non-cardia adenocarcinoma in metformin users compared with non-users in the diabetes cohort**

| Age | Sensitivity analysis 1 (N = 355,461) | Sensitivity analysis 2 (N = 495,822) | Sensitivity analysis 3 (N = 14,221) | Sensitivity analysis 4 (N = 206,769) |
|-----|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
|     | Non-users                          | Metformin users                   | Non-users                          | Metformin users                   |
|    ≤60|                                     |                                   |                                    |                                   |
| Non-users | 103 | Reference | Reference | 137 | Reference | Reference |
| Metformin users | 258 | 0.91 (0.72–1.15) | 0.95 (0.75–1.21) | 374 | 0.91 (0.75–1.11) | 0.95 (0.78–1.17) |
|    >60|                                     |                                   |                                    |                                   |
| Non-users | 70 | Reference | Reference | 55 | Reference | Reference |
| Metformin users | 163 | 0.85 (0.64–1.12) | 0.90 (0.68–1.20) | 258 | 0.92 (0.76–1.11) | 0.92 (0.75–1.13) |

HR: hazard ratio, CI: confidence interval
*Adjusted for sex, age, calendar year, use of non-steroidal anti-inflammatory drugs or aspirin, use of statins, Charlson comorbidity index and Helicobacter pylori eradication treatment
†Restricted to prevalent metformin users as the exposed group
‡Restricted to participants who were followed up for at least 1 year
§Restricted to participants who had received Helicobacter pylori eradication therapy
¶Restricted to participants who had diagnoses of type 2 diabetes only throughout the follow-up period
