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DIABETES, METFORMIN AND GASTRIC ADENOCARCINOMA

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Diabetes, metformin and gastric adenocarcinoma

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The aim of medical science is to delay death.

Therefore, even doctors die.

However, their thesis would be immortal, intact and unread.

------- ~~Jiaojiao Zheng~~ the Anonymous

POPULAR SCIENCE SUMMARY OF THE THESIS

What is known?

Gastric cancer (equivalent to 'stomach cancer') is one of the top 5 most common cancers globally. One in 33 men and 1 in 78 women develop gastric cancer over a lifetime. The most common (>90%) histological subtype of gastric cancer is gastric adenocarcinoma. The word 'adenocarcinoma' represents cancer developing from glands (a type of normal human tissue) or having glandular structures. There are many risk factors for developing gastric cancer, including certain lifestyle habits such as smoking and physical inactivity, dietary factors such as high consumption of salt and pickled food, and infection of a specific bacteria named *Helicobacter pylori*. However, not all cases of gastric cancer could be explained by these factors, and more investigation is needed to understand the causes of this cancer. When occurring, the early symptoms of gastric cancer are often atypical (e.g. fatigue, loss of appetite), making early diagnosis very difficult and thus most patients are diagnosed at an advanced stage. As a result, the survival of patients with gastric cancer is generally not good; most patients die within 5 years after diagnosis. Hence, it is also vital to discover factors that could help improve the survival of gastric cancer.

Diabetes is a common and chronic disease that is characterized by high blood sugar (glucose) levels. Diabetes could cause diseases in various organs, e.g. cardiovascular disease, kidney disease, eye disease, and foot ulcers. Recent studies have shown that diabetes may also be associated with occurrence of different cancers. However, whether diabetes is associated with gastric cancer is not clear because the results from previous studies are not consistent. Metformin is an oral glucose-lowering medication used among most adults with newly diagnosed diabetes. Interestingly, metformin has been found to have beneficial 'side effects' which may prevent against cancer development. The questions are whether metformin protects against the development of gastric cancer or improves the survival of it.

What has been done?

This thesis includes four so-called 'cohort studies' (Study I, III-V) and one so-called 'systematic review and meta-analysis' (Study II). In cohort studies, we identify a specific large group of people and obtain some information (e.g. diabetes status or use of metformin) from them at a specific time. Then we follow them up over a period, usually several years or decades, and wait to see if they develop a disease under study (e.g. gastric cancer) or have an event under study (e.g. death due to gastric cancer). Thanks to the high-quality Swedish health data registries, we did not have to follow every one of the cohorts in person for decades, but only needed to apply for necessary data from the registries. On the other hand, the systematic review with meta-analysis is a scientific way to summarize all relevant existing evidence and integrate the evidence with a mathematic transformation.

What is added by this thesis?

In general, the studies in this thesis aimed to answer the following four questions, and the short answers are provided below:

a) Does diabetes/high blood glucose levels increase the risk of developing gastric cancer? (**Study I and II**)
   *Answer: Diabetes may not increase the chance of getting gastric cancer, but **long-term** high blood glucose levels may do so.*
b) If a diabetes patient is diagnosed with gastric cancer, does diabetes influence his/her survival in gastric cancer? (**Study III**)
   Answer: Patients who have diabetes may have shorter survival in gastric cancer.
c) Does taking metformin prevent the development of gastric cancer? (**Study IV**)
   Answer: No, taking metformin may not help to prevent gastric cancer.
d) Does taking metformin improve the survival in gastric cancer? (**Study V**)
   Answer: Yes, patients taking metformin seem to have a better chance of survival in gastric cancer.

科普小结

研究背景

胃癌是世界常见五大肿瘤之一。每 33 名男性及每 78 名女性中就有一人会罹患胃癌。胃癌最常见的病理类型是“腺癌”，意思是从腺体（一种正常人体组织）发展出的具有类似腺体结构的肿瘤。胃癌发生的危险因素有许多，包括不良的生活习惯如吸烟和缺乏运动等，饮食因素如长期大量摄入盐及腌制食物等，以及感染一种特殊细菌（幽门螺旋杆菌）。尽管如此之多的胃癌危险因素已为人所识，并非所有胃癌的发生都可以被这些因素所解释。因此，科研人员正通过更多的研究以期了解胃癌发生的机制。早期胃癌的症状并不明显， 常见症状有乏力及食欲不振等。因此胃癌的早期诊断十分困难，而大部分患者在确诊时已是肿瘤晚期。这些病人的生存及预后通常不佳，大部分患者会在确诊后 5 年内死亡。因此，科研人员也致力于研究发现任何有助于改善胃癌患者预后的方法。

糖尿病是一种常见的慢性疾病，它的主要症状是血糖的不正常升高。糖尿病还会引发其他器官的疾病，如心血管疾病，肾脏疾病，眼部病变及足部溃疡等。最新的研究表明糖尿病也可能和多种肿瘤的发生相关。但是糖尿病是否和胃癌的发生相关目前尚无定论，且现有研究的结果并不一致。二甲双胍是一种口服降糖药，几乎所有新确诊的糖尿病成年患者都会服用二甲双胍。最近，二甲双胍被发现有一个有意思的 “副作用”，即它有可能可以抑制肿瘤的发展。因此，二甲双胍也有可能可以抑制胃癌的发生或者改善胃癌患者预后。

这本论文里包含了什么研究？

本论文共涵盖 4 个“队列研究”，也即第一个研究以及第三至五个研究，以及一个“系统评价及荟萃分析”，即第二个研究。在队列研究中，研究者们需要找到特定的一大群人，并在一个时间点上获取一些他们的相关信息（例如他们是否有糖尿病或者是否正在使用二甲双胍）。然后对他们进行追踪随访，通常随访的时间可长达几十年，并在此期间观察他们是否会患上某些特定疾病（例如胃癌），或者发生某些特定事件（例如死于胃癌）。得益于瑞典高质量的健康数据登记系统，本论文的研究者并不需要花费数十年去追踪随访研究人群，而仅需向相关的健康数据登记系统管理机构申请所需的数据即可。另一方面，系统评价及荟萃分析是一种特殊的可以总结所有现有证据并通过特定的统计学方法将这些证据汇总的研究。

这些研究回答了什么问题？

总体而言，本论文的研究旨在回答以下四个问题。

1） 糖尿病或者高血糖是否增加罹患胃癌的风险？（第一个研究和第二个研究）

答案：糖尿病本身可能不会增加胃癌风险（第一个研究），但是长期血糖升高却有可能会使胃癌风险增加（第二个研究）。

2） 如果一个糖尿病患者被确诊了胃癌，糖尿病是否会影响这个患者的胃癌生存？(第三个研究)

答案：会，同时患有糖尿病和胃癌的患者的生存时间更短。

3） 服用二甲双胍是否有助于减少得胃癌的几率？（第四个研究）

答案：不，服用二甲双胍对于预防胃癌可能无济于事。

4） 服用二甲双胍是否可以提高患有糖尿病的胃癌患者的生存机会？（第五个研究）

答案：是的，服用二甲双胍的患者的死亡风险更低。

ABSTRACT

Diabetes may increase the risk and mortality of certain cancers, but its association with gastric adenocarcinoma is not clear. On the other hand, metformin, a first-line treatment for diabetes, may reduce cancer risks and improve cancer-related survival, but these associations have not been confirmed in gastric adenocarcinoma as well. The aim of this thesis is to evaluate if and how diabetes or its biomarkers and the use of metformin influence the risk and prognosis of gastric adenocarcinoma.

Study I investigated if diabetes or prediabetes influenced the risk of gastric adenocarcinoma in a population-based Swedish cohort. Participants of the Northern Swedish Health and Disease Study were included and followed up from 1985 to 2017. Participants exposed to diabetes or prediabetes, as confirmed by self-reports or oral glucose tolerance tests, were compared with those of normoglycaemia for the incidence of gastric adenocarcinoma, identified from the Swedish Cancer Registry. Cox proportional hazard regression analyses with adjustment for sex, age, calendar year, body mass index, tobacco smoking, and education level showed no associations between prediabetes or diabetes and the risk of gastric adenocarcinoma (hazard ratio [HR] 1.07, 95% confidence interval [CI] 0.79-1.44 for prediabetes; HR 0.77, 95% CI 0.46-1.29 for diabetes).

Study II was a systematic review and meta-analysis assessing associations between serum Haemoglobin A1c (HbA1c) or glucose and the risk of developing gastric cancer, based on studies identified from three databases: MEDLINE, Embase and Cochrane library. The random-effects model showed that elevated levels of serum HbA1c were associated with an increased risk of gastric cancer (pooled HR 1.36, 95% CI 1.06-1.74), but not so for elevated levels of serum glucose (pooled HR 1.11, 95% CI 0.98-1.26).

Study III was a population-based cohort study evaluating whether diabetes worsened the prognosis in gastric adenocarcinoma, including all patients diagnosed with gastric adenocarcinoma between 1990 and 2014 in Sweden. Co-existing diabetes at diagnosis of gastric adenocarcinoma was analysed by the Cox proportional hazard regression with the risk of mortality due to gastric adenocarcinoma (disease-specific mortality) as well as all-cause mortality. The HRs were adjusted for sex, age, calendar year, and co-morbidity. Patients with diabetes at diagnosis had a moderately increased risk of disease-specific mortality compared with those without diabetes (HR 1.17, 95% CI 1.11-1.22). Besides, diabetes was also associated with an increased risk of all-cause mortality among patients who underwent gastrectomy for gastric adenocarcinoma (HR 1.23, 95% CI 1.10-1.38).

Study IV was a population-based cohort study assessing whether metformin use decreased the risk of gastric adenocarcinoma. All data were retrieved from four national health data registries and participants were selected from users of certain commonly prescribed medications. Two sub-cohorts were established, a diabetes cohort and a matched cohort. Cox proportional hazard regressions with adjustment for sex, age, calendar year, comorbidity, *Helicobacter pylori* eradication treatment, use of non-steroidal anti-inflammatory drugs, and

use of statins were used to compare users and non-users of metformin in relation to the risk of gastric non-cardia and cardia adenocarcinoma. The risk of gastric non-cardia adenocarcinoma was not decreased among metformin users compared with non-users in either sub-cohorts (HR 0.93, 95% CI 0.78-1.12 in the diabetes cohort; HR 1.30, 95% CI 1.18-1.42 in the matched cohort). Besides, metformin use did not decrease, but rather increased the risk of gastric cardia adenocarcinoma in either sub-cohorts (HR 1.49, 95% CI 1.09-2.02 in the diabetes cohort; HR 1.58, 95% CI 1.38-1.81 in the matched cohort).

Study V was a population-based cohort study aiming to test if pre-diagnosis use of metformin improved the prognosis in gastric adenocarcinoma. The study included all diabetes patients who were diagnosed with gastric adenocarcinoma between 2005 and 2018. Associations between metformin use within two years before the diagnosis of gastric adenocarcinoma and the risk of disease-specific and all-cause mortality were analysed with Cox proportional hazard regressions, with adjustment for sex, age, calendar year, comorbidity, use of non-steroidal anti-inflammatory drugs, and use of statins. Metformin use was associated with a decreased risk of disease-specific mortality (HR 0.79, 95% CI 0.67-0.93) and all-cause mortality (HR 0.78, 95% CI 0.68-0.90) among diabetes patients with gastric adenocarcinoma.

To conclude, diabetes or prediabetes did not increase the risk of gastric adenocarcinoma in the Swedish population of Study I, but aggregated evidence indicated that long-term hyperglycaemia may increase the risk of gastric cancer (Study II). Gastric adenocarcinoma patients with co-existing diabetes had a higher risk of disease-specific mortality compared with those without diabetes (Study III). Besides, although metformin use might not prevent gastric adenocarcinoma (Study IV), it may improve the prognosis of this cancer among diabetes patients (Study V).

LIST OF SCIENTIFIC PAPERS

I. Jiaojiao Zheng, Martin Rutegård, Giola Santoni, Bengt Wallner, Ingegerd Johansson, Malin Sund, Shao-Hua Xie and Jesper Lagergren
Prediabetes and diabetes in relation to risk of gastric adenocarcinoma
Br J Cancer *2019 Jun;120(12):1147-1152.*

II. Jiaojiao Zheng, Yunhe Gao, Shao-Hua Xie, Giola Santoni, and Jesper Lagergren
Haemoglobin A1c and serum glucose levels and risk of gastric cancer: A systematic review and meta-analysis
Manuscript submitted.

III. Jiaojiao Zheng, Shao-Hua Xie, Giola Santoni, and Jesper Lagergren
Population-based cohort study of diabetes mellitus and mortality in gastric adenocarcinoma
Br J Surg *2018 Dec;105(13):1799-1806.*

IV. Jiaojiao Zheng, Shao-Hua Xie, Giola Santoni, and Jesper Lagergren
Metformin use and risk of gastric adenocarcinoma in a Swedish population-based cohort study
Br J Cancer *2019 Nov;121(10):877-882.*

V. Jiaojiao Zheng, Giola Santoni, Shao-Hua Xie, and Jesper Lagergren
Improved prognosis in gastric adenocarcinoma among metformin users in a population-based study
Br J Cancer *(in press).*

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LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical Classification
BMI	Body mass index
CCI	Charlson Comorbidity Index
CI	Confidence interval
DDD	Defined Daily Dose
HbA1c	Haemoglobin A1c
HR	Hazard ratio
H. pylori	*Helicobacter pylori*
ICD	International Classification of Diseases
IGF	Insulin-like growth factor
MONICA	Monitoring Trends and Determinants in Cardiovascular Disease Project
NSAID	Non-steroidal anti-inflammatory drug
NSHDS	Northern Sweden Health and Disease Study
OGTT	Oral glucose tolerance test
RCT	Randomized controlled trial
VIP	Västerbotten Intervention Program
WHO	World Health Organization

1 INTRODUCTION

Diabetes is a chronic disease with increasing prevalence. The traditional classification of diabetes is type 1 diabetes, type 2 diabetes, gestational diabetes, and other types of diabetes. Hyperglycaemia is the common hallmark for all diabetes, which could lead to disorders in multiple organs. Metformin is a commonly prescribed medication that decreases the serum levels of glucose and insulin, and is used as a first-line treatment for type 2 diabetes.

Gastric cancer is one of the most common malignancies worldwide. Many risk factors have been identified for gastric cancer but its aetiology has not been fully understood. Major treatments for gastric cancer include gastrectomy, chemotherapy, or a combination of both. Despite these treatments, the prognosis of gastric cancer is generally poor, adding huge burdens to the patients, public health, and society.

In clinical practice, gastric adenocarcinoma (the main histological type of gastric cancer) is often diagnosed in a patient with diabetes. Several studies have shown that diabetes may increase the risk of several cancers and also influence cancer-related survival. On the other hand, metformin has been found to have anti-cancer effects and is associated with decreased cancer risk and improved cancer prognosis. However, previous studies have provided inconsistent results on the associations between diabetes or metformin and gastric adenocarcinoma.

The four population-based cohort studies and one systematic review and meta-analysis included in this thesis aimed to clarify associations between these two diseases. Specifically, Study I and II evaluated whether diabetes, prediabetes, or their biomarkers, i.e. serum Haemoglobin A1c (HbA1c) or glucose, are associated with an increased risk of developing gastric adenocarcinoma. Study III assessed the influence of co-existing diabetes on the disease-specific mortality among patients with gastric adenocarcinoma. Study IV addressed the question whether metformin use prevents the development of gastric adenocarcinoma. And Study V investigated the potential role of pre-diagnosis use of metformin in the prognosis of gastric adenocarcinoma among diabetes patients.

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2 LITERATURE REVIEW

2.1 DIABETES

2.1.1 Overview

Diabetes is an ancient disease, the first record of which could be traced back to 1500. The first diagnostic criteria for diabetes were developed in 1979.[1, 2] Over the past two centuries, it has been gradually recognized that diabetes represents a group of disorders affecting multiple organs of the human body. Diabetes is characterized by hyperglycaemia and is traditionally classified as type 1 diabetes, type 2 diabetes, gestational diabetes, and other types of diabetes. Prediabetes is a preclinical and asymptomatic stage of impaired glucose tolerance or impaired fasting glycaemia and is a high-risk state of developing diabetes.[3]

2.1.2 Epidemiology and treatment

Type 1 diabetes is a heritable disorder due to autoimmune destruction of pancreatic β cells, resulting in insulin deficiency and chronic hyperglycaemia.[4] Most patients with type 1 diabetes are diagnosed before adulthood and exogenous insulin replacement is immediately needed.[5] Both the prevalence and incidence of type 1 diabetes are increasing globally, but with great variations among different countries.[6-8] The discovery and application of insulin (and its analogues) are the milestones in the treatment of type 1 diabetes, and remain so although many other therapies have been explored.[4, 9]

Type 2 diabetes is caused by pancreatic β-cell dysfunction and insulin resistance, leading to progressive hyperglycaemia. The population living with diabetes has been nearly quadrupled from 1980 to 2014, with around 90% of them having type 2 diabetes.[10, 11] The increasing prevalence of type 2 diabetes is a combined effect of increased obesity, changes in lifestyle, and an aging population over the world.[11] The treatment for type 2 diabetes includes lifestyle interventions, glycaemic control, and management of complications. At diagnosis, patients with type 2 diabetes usually remain around 20% of the pancreatic β-cell function. Thus, lifestyle interventions and oral glucose-lowering medications are usually the first-line treatments. However, with the continuous decline of β-cell function, most patients eventually need insulin to regulate their blood glucose.[11, 12] A wide range of medications is available for type 2 diabetes treatment with a similar effect of lowering blood glucose, but their effect on circulating insulin is different. Exogenous insulin, insulin analogues, and sulfonylureas increase the circulating insulin levels; metformin and thiazolidinedione decrease circulating insulin levels; acarbose, glucagon-like peptide-1, and sodium-glucose linked transporter-2 inhibitors have no clear effect on insulin levels; while dipeptidyl peptidase-4 has a complex effect of simultaneously decreasing insulin resistance and increasing insulin secretion.[13, 14] Compared with patients without diabetes, diabetes patients have an increased risk of overall mortality, and cardiovascular diseases are the main causes of death.[15]

2.2 DIABETES AND CANCER

2.2.1 Diabetes and risk of cancer

Many studies have shown that diabetes is associated with an increased overall cancer risk.[16-19] The influence of diabetes on cancer risk might be explained by two hypothesized mechanisms: 1) a direct pathway through the pathological changes following hyperglycaemia and hyperinsulinemia, and 2) an indirect pathway through shared risk factors for diabetes and cancer, e.g. aging, obesity, smoking, and dietary factors.[20-22] Although the second hypothesis seems plausible, it is unlikely to explain all of the associations between diabetes and cancer risks, because these risk factors are also common in other diseases, e.g. hypertension, for which no increased cancer risks have been found.

It has been proposed that the insulin/insulin-like growth factor (IGF) axis plays a key role in the carcinogenesis among diabetes patients. Insulin is a peptide hormone produced by pancreatic β-cells, and IGFs are polypeptides with structures resembling the structure of proinsulin.[23, 24] Both insulin and IGFs are regulators of growth and energy metabolism. High concentrations of insulin activate IGF-I receptors and increase IGF-I bioavailability. The downstream of IGF-I receptors is the Akt and AMPK signalling networks that regulate the proliferation and apoptosis of cancer cells.[23, 24] Besides, IGFs also interact with certain cancer-related molecules, including oestrogen, epidermal growth factor, interleukin-6, and tumour necrosis factor-α.[20]

2.2.2 Diabetes and prognosis of cancer

At cancer diagnosis, around 8% to 18% of patients have pre-existing diabetes, and among elderly cancer patients, the prevalence is even higher.[25-27] A meta-analysis showed an increased risk of all-cause mortality (hazard ratio [HR] 1.41, 95% confidence interval [CI] 1.28-1.55) among diabetic cancer patients compared with non-diabetic cancer patients.[25] But all-cause mortality cannot be directly related to cancer-related survival in these patients, since diabetes is known to also increase the risk of death from many other causes.[15] Studies evaluating the effect of diabetes on cancer-specific mortality are limited and the existing studies usually aggregated in certain cancer types whose risk is increased among diabetes patients.[21, 28] Diabetes may influence the survival of cancer patients at different stages, including cancer screening, cancer detection, selection for curative surgery, postoperative short-term mortality, selection for adjuvant therapy, choice of dose and regimen for chemotherapy, response to systemic treatment, chemotherapy-related toxicity, and cancer recurrence.[28, 29]

2.2.3 Metformin and cancer

Metformin is the most widely evaluated anti-diabetes medication for its influence on cancer risk and survival. Most studies have examined cancers of the colorectum, prostate, and breast.[30] The potential anti-cancer mechanisms of metformin include the direct activation of the AMPK pathway and indirect effects from lowering the circulating glucose and insulin levels.[31] Besides, metformin may also increase the response rate to chemotherapies.[28] When evaluating metformin studies, three specific methodological considerations should be taken into account. First, time-related bias, especially immortal time bias, are prominent in metformin studies and may exaggerate the protective effects of metformin.[32] Second, confounding by indication may exist when the comparison is made among users of different anti-diabetes drugs. Third, dosages, cumulative duration of use, and exposure to other medications should be considered when interpreting the results.[20, 33-36]

2.3 GASTRIC ADENOCARCINOMA

2.3.1 The stomach

The stomach is a j-shaped, muscular, hollow, and distensible organ located mainly on the left side of the upper abdominal cavity. It connects the distal oesophagus and the duodenum and is divided into four sections: cardia, fundus, body, and pylorus (Figure 1).[37] The core function of the stomach is early-stage digestion during which the stomach works as a reservoir to store food, a factory to produce acids, hormones, and enzymes, as well as an engine to pulverize and transport food.[38]

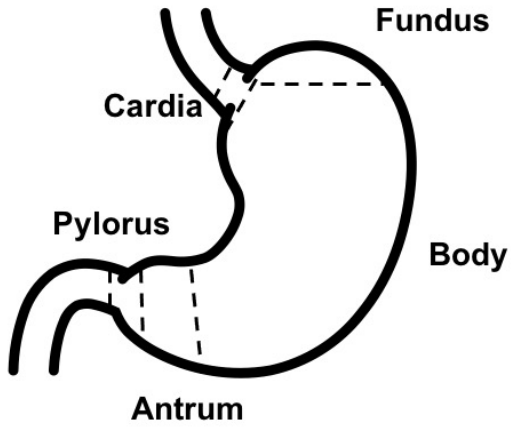

Figure 1. Sections of the stomach. Illustration by the author ©

2.3.2 Gastric cancer: Occurrence and classification

Cancer of the stomach is also called gastric cancer and is an important component of the global cancer burden. In 2017, gastric cancer caused 19.1 million disability-adjusted life-

years (DALYs), accounting for 8.2% of the total DALYs caused by all cancers.[39] In 2020, gastric cancer was the 5th most common cancer and the 3rd leading cause of cancer deaths.[40] Between 2006 and 2016, the overall incidence of gastric cancer increased by 15%, which was mainly attributed to a change in the population age structure and population growth.[41] The incidence of gastric cancer differs markedly between geographical areas, with the highest rates in Eastern Asia and lowest in Northern America, Northern Europe, and most countries in Africa.[42]

There are different approaches to classify gastric cancer into different subtypes. Anatomically, most (73%) gastric cancers are non-cardia cancer, whereas 27% are cardia cancers, i.e. locating close to the gastro-oesophageal junction.[43] Gastric non-cardia and cardia cancers have different aetiology, geographical distribution, disease courses, and clinical treatment.[44] During the past few decades, the incidence of gastric non-cardia cancer has decreased, while the incidence of gastric cardia cancer has been stable or increased.[45] Histologically, 95% of gastric cancers are adenocarcinomas, which means that the cancer originates from cells that line glands and make mucus. The development of gastric adenocarcinoma goes through a stepwise transition from normal mucosa through chronic atrophic gastritis and intestinal metaplasia, to dysplasia and carcinoma, also known as the Correa's cascade.[46]

2.3.3 Gastric cancer: Risk factors

Many factors are involved in the development of gastric adenocarcinoma (Figure 2). Chronic atrophic gastritis, intestinal metaplasia, gastric ulcers, gastric polyps, previous gastric surgery (gastrectomy), and Ménétrier's disease are preconditions that are associated with an increased risk of developing gastric adenocarcinoma.[47] Aging, male sex, tobacco smoking, and family history are common risk factors for both gastric cardia and non-cardia adenocarcinoma.[48] *Helicobacter pylori* (*H. pylori*) infection is the most important risk factor for gastric non-cardia adenocarcinoma.[49] *H. pylori* infection triggers the Correa's cascade and promotes gastric atrophy and intestinal metaplasia. Other risk factors for non-cardia gastric adenocarcinoma include a sedentary lifestyle, low socioeconomic status, high intake of salt and pickled food, as well as low consumption of fresh fruits and vegetables.[48] Different from gastric non-cardia adenocarcinoma, gastric cardia adenocarcinoma is closely associated with obesity and gastro-oesophageal reflux diseases.[48]

Figure 2. Some important risk factors (male sex, obesity, tobacco smoking, salt consumption, pickled food, and *H. pylori* infection) for gastric cancer. Illustration by the author ©

2.3.4 Gastric cancer: Treatment and prognosis

Early-stage gastric adenocarcinomas are usually asymptomatic and most patients with gastric adenocarcinoma are therefore diagnosed at an advanced stage. The most common symptoms are anorexia, dyspepsia, weight loss, vomiting, and abdominal pain.[50] In most cases, gastric adenocarcinoma is diagnosed by histological examination of biopsies at gastroscopy.[51] Treating gastric adenocarcinoma incorporates a multidisciplinary approach involving gastroenterologists, surgeons, oncologists, pathologists, radiologists, and dietitians.[52] At present, radical surgical resection is the mainstay of curative treatment for gastric adenocarcinomas, while for selected early-stage cases, endoscopic resection is also curative.[53] For patients with resectable gastric adenocarcinoma of stage IB-III, preoperative chemotherapy followed by gastrectomy and D2 nodal dissection is recommended, and the laparoscopic approach is gaining popularity over open surgery.[53] Adjuvant chemotherapy and chemo-radiotherapy may also improve overall survival in addition to gastrectomy in some cases. For patients with unresectable or metastatic gastric adenocarcinoma, systemic chemotherapy can improve survival and quality of life.[53] The prognosis of gastric adenocarcinoma is poor in most countries. The global 5-year survival for gastric adenocarcinoma is generally between 20%-30%, with the exception of some high-risk areas (Japan and Korea) where endoscopic screening is performed routinely and gastric adenocarcinoma is often diagnosed at an early stage.[54] In Sweden, the 5-year survival is around 18% for both gastric non-cardia and cardia adenocarcinoma.[55]

2.4 DIABETES AND RISK OF GASTRIC ADENOCARCINOMA

Previous studies investigating associations between diabetes and gastric adenocarcinoma have provided inconsistent results. Some studies found that diabetes increased the risk of

gastric adenocarcinoma, while no association was indicated in other studies.[56-59] There are several explanations for the inconsistency, e.g. the heterogeneity of study populations, the methods of measurement of diabetes, the length of follow-up, and the adjustment for confounders. In a systematic review and meta-analysis pooling results from 12 studies, a stronger association between diabetes and risk of gastric adenocarcinoma was found in East Asian populations compared with Western populations.[60] An influence of sex on the relation between diabetes and risk of gastric adenocarcinoma was also reported in several studies, but again with inconsistent results.[61-64] Besides, the excess risk of gastric adenocarcinoma due to diabetes may not be constant over time. While the increased risk of gastric adenocarcinoma among diabetes patients during the early follow-up may be explained by detection bias,[63] a study from Taiwan showed that diabetes increased the risk of gastric adenocarcinoma only after 5 years of follow-up,[58] suggesting an association between diabetes duration and risk of gastric adenocarcinoma.

Few studies have evaluated the associations between diabetes and risk of gastric non-cardia and cardia adenocarcinomas separately. One study from the United States reported that self-reported diabetes was associated with an increased risk of gastric cardia adenocarcinoma, while a study from Korea found no increased risk of either gastric cardia or non-cardia adenocarcinoma related to diabetes.[65, 66] Studies from Western countries have reported an increased risk of gastric adenocarcinoma specifically among type 1 diabetes patients, and a meta-analysis has summarized the increased relative risk of 41%.[56, 67-71] Yet, the number of relevant studies of type 1 diabetes is limited and more observational studies are warranted to establish an association in other populations.

The mechanisms of which diabetes may influence gastric carcinogenesis are generally similar to the above-mentioned ones for other cancers. Pre-clinical studies have provided evidence that insulin and exogenous IGFs promoted the proliferation of gastric cancer cells, and overexpression of IGFs has been found in specimens of gastric adenocarcinoma.[72, 73] In addition, inhibition of the IGF signalling pathway reduced the proliferation and invasion of gastric cancer cells.[74]

Diabetes may also act as a co-factor of *H. pylori* infection in the development of gastric adenocarcinoma. A higher prevalence of *H. pylori* infection among diabetic patients compared with non-diabetic controls has been reported in some studies,[75-77] but not others.[78, 79] When compared with non-diabetic controls, diabetes patients were reported to have lower eradication rates and higher re-infection rates of *H. pylori*.[80, 81] A Japanese study reported that coexistence of hyperglycaemia and *H. pylori* infection increased the risk of gastric adenocarcinoma compared with *H. pylori* infection alone, suggesting that hyperglycaemia may modify the carcinogenic effect of *H. pylori*.[82] No difference in risk of gastric adenocarcinoma between diabetic and non-diabetic patients after *H. pylori* eradication was reported in another Japanese study.[83] The interaction between diabetes and *H. pylori* infection may potentially explain why the associations between diabetes and the increased risk of gastric adenocarcinoma were more often reported in Asian populations, where the prevalence

of *H. pylori* infection is higher than elsewhere. However, the interaction between diabetes and *H. pylori* infection in relation to the risk of gastric adenocarcinoma has only been analysed in Japanese populations, and whether this also exists in other populations is not clear.

2.5 DIABETES AND PROGNOSIS OF GASTRIC ADENOCARCINOMA

Few studies have examined the association between diabetes and the prognosis in gastric adenocarcinoma, and most of the available studies were not designed especially for gastric adenocarcinoma. Among studies that have evaluated diabetes and the risk of long-term mortality following the gastric cancer diagnosis, a Swedish study reported an increased risk of gastric-cancer-specific mortality (HR 1.18, 95% CI 1.08-1.29)[84] and a Korean study showed an increased risk of all-cause mortaliy (HR 1.52, 95% CI 1.25-1.84) among diabetes patients compared with non-diabetic patients.[85] The associations between diabetes and postoperative mortality (mostly short-term) after gastrectomy were investigated in some studies. Increased risk of postoperative mortality among patients with diabetes compared with those without was found in one study, but not others.[86-88]

The mechanisms through which diabetes might increase the risk of mortality in gastric adenocarcinoma are less understood. Limited evidence has shown that diabetes seems not to influence the selection for gastrectomy, but increase the risk of postoperative complications.[88, 89] In addition, high glucose levels may increase chemo-resistance among patients with gastric adenocarcinoma.[90] It is still unclear whether pre-existing diabetes influences the detection of gastric adenocarcinoma, application of adjuvant therapy or dose and regimen used for, and the risk of tumour recurrence after gastrectomy.

2.6 METFORMIN AND GASTRIC ADENOCARCINOMA

Studies examining the use of metformin in relation to the risk of gastric adenocarcinoma are limited and their results are not consistent.[91-93] Some studies, mostly from Asian populations, indicated that metformin use decreased the risk of gastric adenocarcinoma.[91, 92, 94] In contrast, studies from Western populations usually did not find any association between metformin use and the risk of gastric adenocarcinoma, which is consistent with the results of a recent meta-analysis.[91, 95, 96] Besides, a reduction in risk of gastric adenocarcinoma was related to the duration of metformin use in a Korean study, suggesting a protective effect among long-term users of metformin.[92] Very few studies have evaluated the role of metformin use in the prognosis of gastric adenocarcinoma. In a systematic review and meta-analysis, no associations were found between metformin use and survival of gastric adenocarcinoma when pooling the results from three cohort studies.[96]

3 RESEARCH AIMS

The overarching aim of this thesis was to assess diabetes mellitus, as well as its treatment metformin, in relation to the risk and prognosis of gastric adenocarcinoma.

The specific aims of the included studies were:

- To evaluate the associations between diabetes or prediabetes and the risk of developing gastric adenocarcinoma
- To summarize the existing evidence assessing the associations between serum levels of HbA1c and glucose and the risk of gastric cancer
- To investigate the influence of pre-existing diabetes on the prognosis in gastric adenocarcinoma
- To assess the association between metformin use and the risk of developing gastric adenocarcinoma
- To explore the influence of metformin use on the prognosis in gastric adenocarcinoma

4 MATERIALS AND METHODS

4.1 OVERVIEW

Table 1. Methods overview of the included studies

	Study I	**Study II**	**Study III**	**Study IV**	**Study V**
Design	Cohort study	Systematic review and meta-analysis	Cohort study		
Population	The Northern Sweden Health and Disease Study cohort	Individuals with objectively measured serum HbA1c or glucose	Patients diagnosed with gastric adenocarcinoma in Sweden	Users of certain commonly prescribed medications in Sweden	Diabetes patients diagnosed with gastric adenocarcinoma in Sweden
Period	1986 - 2017	1972 - 2016	1990 - 2014	2005 - 2015	2005 - 2019
Exposure	Diabetes and prediabetes (self-reported or verified by OGTT[*])	Measured levels of serum HbA1c and glucose	Diagnosed diabetes	Use of metformin	Use of metformin
Outcomes	Gastric adenocarcinoma	Gastric cancer	Gastric-adenocarcinoma-specific mortality and all-cause mortality	Gastric adenocarcinoma	Gastric-adenocarcinoma-specific mortality and all-cause mortality
Statistical analysis	Cox proportional hazard regression	Generic inverse-variance method under a random-effects model	Cox proportional hazard regression, and competing-risks model	Cox proportional hazard regression	Cox proportional hazard regression, and competing-risks model
Covariates	Sex, age (as time scale) calendar year, BMI, tobacco smoking, and education	As assessed in individual studies	Sex, age, calendar year, CCI[†], tumour stage, and gastrectomy	Sex, age, calendar year, CCI[†], use of NSAIDs[‡], use of statins, and *H.* pylori treatment	Sex, age, calendar year, CCI[†], use of NSAIDs[‡], and use of statins
Data sources	Survey data from The Northern Sweden Health and Disease Study; Swedish Cancer Registry; Cause of Death Registry	Medline, Embase, Cochrane Library, and reference lists	Swedish Cancer Registry; Patient Registry; Cause of Death Registry	Swedish Prescribed Drug Registry; Cancer Registry; Patient Registry; Cause of Death Registry	Swedish Prescribed Drug Registry; Cancer Registry; Patient Registry; Cause of Death Registry

[*] OGTT: Oral glucose tolerance test;

[†] CCI: Charlson comorbidity index;

[‡] NSAID: Non-steroidal anti-inflammatory drug

4.2 DATA SOURCES

Study I and III-V were fully or partly based on data retrieved from different Swedish national health data registries, while study I was also based on data from the Northern Sweden Health and Disease Study (NSHDS). The data of study II (a systematic review and meta-analysis) were identified from Embase, Medline, and Cochrane Library.

4.2.1 Swedish Registries

In Sweden, reporting health data to registries is mandatory according to the legislation (1990: 1144 and 1998:543), contributing to the high completeness and quality of these registries. Every Swedish resident is assigned a unique personal identity number upon birth or immigration and this number was used to link individual data between registries. The detailed codes to identify variables in each registry are listed in the supplements.

4.2.1.1 The Cancer Registry

The Swedish Cancer Registry was founded in 1958 and records data related to cancer diagnosis for the whole Swedish population. The data retrieved from the Cancer Registry in this thesis include tumour site, histological type, tumour stage (since 2004), and date of diagnosis. Different versions of the International Classification of Diseases (ICD) have been used for coding cancer diagnosis in the Cancer Registry over time but ICD-7 and WHO/HS/CANC/24.1 are used throughout the periods. Data on tumour stage were available in the registry from 2004 and were reported based either on clinical or pathological evaluations. The register is updated once a year. The completeness of the diagnosis of gastric adenocarcinoma in the Cancer Registry is up to 98% and the positive predictive value is 96%.[97]

4.2.1.2 The Patient Registry

The Swedish Patient Registry collects data on inpatient care throughout Sweden since 1987 and covers specialized outpatient care since 2001. However, data on primary care in Sweden are not included in the Patient Registry. The following information was retrieved from the Patient Registry and utilized in this thesis: disease diagnosis, operation codes, and date of operation. The Swedish version of ICD is used for reporting in the Patient Registry with the Swedish version of ICD-9 from 1987 to 1997, and the Swedish version of ICD-10 afterward. The register is updated monthly. The diagnosis of diabetes in the Patient Registry is around 88% complete when compared with the diabetes quality registry.[98] For other diseases, the quality of the diagnosis data from the inpatient care is generally good, with the positive predictive values varying between 85 and 95%.[99]

4.2.1.3 The Cause of Death Registry

The Swedish Cause of Death Registry records data on date and causes of death from death certificates for all Swedish residents since 1952. Different versions of ICD (6-10) have been

used for reporting causes of death over time. The Cause of Death Registry is updated once a year for cause of death and continuously for date of death, with high completeness for the number of deaths (>99%) and underlying causes of death (96%).[100]

4.2.1.4 The Prescribed Drug Registry

The Swedish Prescribed Drug Registry is among the youngest registries in Sweden, implemented in July 2005. Data on all prescribed and dispensed drugs from pharmacies are recorded in this registry, accounting for 84% of the total drug sales in Sweden. The remaining 16% are drugs sold over-the-counter or used in hospitals or nursing homes.[101] Around 65%-67% of the Swedish population have at least one record in the Prescribed Drug Registry every year.[102, 103] The register is updated monthly. All dispensed drugs in the Prescribed Drug Registry are coded with the Anatomical Therapeutic Chemical (ATC) Classification and defined daily dose (DDD) is used for counting the amount of drug consumption. The data quality in the Prescribed Drug Registry is generally good since the data are collected electronically and checked by the Swedish eHealth Agency before recorded.

4.2.2 Northern Sweden Health and Disease Study (NSHDS)

The NSHDS is a biobank with survey data from three sources: The Västerbotten Intervention Program (VIP) cohort, the Northern Sweden Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) cohort, and the Mammography Screening Project cohort. Study I was based on the VIP and MONICA cohorts. The VIP is an ongoing intervention program aiming at reducing morbidity and mortality from cardiovascular disease and diabetes. Each year, all residents living in the county of Västerbotten who turn 40, 50, or 60 years of age are invited to participate the program, which involves a comprehensive survey and screening for risk factors for cardiovascular disease and diabetes, followed by individual counselling.[104] The MONICA is a World Health Organization (WHO) program evaluating risk factors for cardiovascular disease in relation to mortality trends. Residents from counties of the Norrbotten and Västerbotten are randomly selected and stratified for sex and age groups to attend the program. The participants are asked to complete questionnaires, and physical examinations are performed by trained survey teams.[105] The MONICA surveys have been conducted recurrently for six times and the latest one was in 2009.

The VIP and MONICA programs are similar regarding the geographic settings, overlapping participants, recruitment periods (VIP from 1985 and MONICA from 1986), evaluation of lifestyle and dietary habits, and oral glucose tolerance tests (OGTT). These similarities contribute to the feasibility to combine data from these two programs for Study I.

4.3 STUDY DESIGN

4.3.1 Study I

4.3.1.1 Design

Study I was a cohort study based on the NSHDS (VIP and MONICA) between 1985 and 2017 investigating whether prediabetes or diabetes increased the risk of gastric adenocarcinoma. The exposures were classified as prediabetes, diabetes or both. Prediabetes and diabetes were defined by OGTT results according to the WHO standards. Participants with self-reported diabetes in the questionnaire were also included in the diabetes group. The outcome was gastric adenocarcinoma occurring during the follow-up. The eligible participants from VIP and MONICA were included in the study from the date of their first physical assessment and followed up until the diagnosis of gastric adenocarcinoma, death, or end of the study period (27th April 2017), whichever occurred first. During the follow-up, the exposure status was allowed to change as follows: from normal blood glucose ('normoglycaemia') to prediabetes, from normoglycaemia to diabetes, from prediabetes to diabetes, and from prediabetes to normoglycaemia.

4.3.1.2 Statistical analysis

Cox proportional hazard regression was used to analyse the associations between diabetes or prediabetes and the risk of gastric adenocarcinoma, providing HRs with 95% CIs. Attained age was the time scale and thus adjusted for in all analyses. Twelve covariates were considered as potential confounders: age, sex, calendar year of inclusion, body mass index (BMI), tobacco smoking, alcohol consumption, education level, marital status, physical activity level, intake of fruit and vegetables, daily salt intake, and daily energy intake. After a stepwise backward selection, only covariates that changed the estimates for at least 10% were kept in the model. The covariates remained in the final model were sex, calendar year of inclusion (1986–1994, 1995–2003, or 2004–2017), BMI (in tertiles), tobacco smoking (never smoker, ex-smoker, or current smoker), and education level (compulsory school or less, upper secondary school, or college or postgraduate level).

The analyses were conducted separately comparing prediabetes status, diabetes status, or any of the former two with normoglycaemic status in relation to the risk of developing gastric adenocarcinoma. Besides, linear associations between the continuous fasting glucose or 2-h post-load glucose levels and the risk of gastric adenocarcinoma were tested. The Schoenfeld residuals were used to test the proportionality assumption and the assumptions were met for all analyses.

4.3.2 Study II

4.3.2.1 Design

Study II was a systematic review and meta-analysis evaluating the existing evidence on the associations between serum levels of HbA1c or glucose and the risk of gastric cancer. Three

databases were searched with predefined search strategies: MEDLINE, Embase, and Cochrane Library. The first search was conducted in December 2019, and an update was carried out in January 2021. Reference lists of relevant articles were also searched manually. Two authors independently reviewed and screened for studies available in the English language, where HbA1c or glucose was measured before the occurrence of gastric cancer and estimates for the risk of gastric cancer were reported. When studies were based on overlapped study populations, only the one with the largest sample size was included. However, studies based on the same population that separately analysed HbA1c and glucose were regarded as two individual studies and were both included. All included studies went through independent quality assessment by two authors using a modified Newcastle-Ottawa Scale for cohort studies. If any disagreement occurred during the process, a third author was consulted.

4.3.2.2 Statistical analyses

The meta-analysis was conducted with a random-effects model using the generic inverse-variance method and pooled HR was the risk estimate. For studies reporting serum HbA1c, the cut-off value was set at 6%. For studies reporting serum glucose, the cut-off values varied a lot in individual studies and the highest level was compared with the lowest. When appropriate, in studies using quartile or quintile cut-off values, the estimates were converted to a value that was equivalent to the tertiles to reduce heterogenity.[106]

Cochran's Q test and I^2 statistics were used to assess the heterogeneity of the included studies. For Cochran's Q test, a *P* value <0.1 was considered significant, and for I^2 statistics, ≤25% was considered low heterogeneity, 25%-49% moderate heterogeneity, and ≥50% high heterogeneity. Subgroup analyses by different study characteristics, i.e. sex, geographic area (Asian or non-Asian), risk of bias, adjustment for BMI (obesity), and adjustment for *H. pylori* infection, were used to identify potential sources of heterogeneity. Regarding publication bias, visual inspection of funnel plots was first used, followed by Egger's test if asymmetry was identified, and a nonparametric trim-and-fill analysis if Egger's test showed significant results.

4.3.3 Study III

4.3.3.1 Design

Study III was a population-based cohort study in Sweden, aiming at investigating whether diabetes increased the risk of mortality in gastric adenocarcinoma. The total cohort included all diagnosed gastric adenocarcinoma patients in Sweden between 1990 and 2014. Based on the total cohort, two sub-cohorts were constructed, one including only patients with gastric non-cardia adenocarcinoma (the non-cardia sub-cohort), and the other one including only patients who underwent gastrectomy for gastric adenocarcinoma (the surgical sub-cohort). The exposure was coexisting diabetes diagnosed before or at the diagnosis of gastric adenocarcinoma. The primary outcome was mortality due to gastric adenocarcinoma (disease-specific mortality), but in the surgical sub-cohort, the outcome was all-cause mortality after gastrectomy. The participants were followed up from the diagnosis date of

gastric adenocarcinoma until death or end of the study (31st December 2014). All data were retrieved from the following three registries: the Swedish Cancer Registry, Patient Registry, and Cause of Death Registry.

4.3.3.2 Statistical analyses

Cox proportional hazard regression was used to analyse differences in risk of mortality comparing patients with and without diabetes, providing HRs with 95% CIs. In the analyses of the total cohort and the non-cardia sub-cohort, a multivariable model adjusted for sex, age at diagnosis, and calendar year of diagnosis was applied. In the analyses of the surgical sub-cohort, the multivariable model was further adjusted for comorbidities, represented by the Charlson Comorbidity Index (CCI), a well-validated numeric tool to summarize the number and severity of certain groups of comorbidities.[107] The CCI was scored as 0, 1, or ≥2 throughout this thesis. The total cohort and the non-cardia sub-cohort were analysed separately for the entire follow-up, while the surgical sub-cohort was analysed with stratification of the postoperation periods (30 days, 90 days, 6 months, and 12 months). Besides, the total cohort was further stratified by CCI scores, gastrectomy, and tumour stage (I-II or III-IV). The proportionality assumption was tested by checking the log-log plots and was met in all analyses except for the stratified analysis by tumour stage. Therefore, the risk of mortality within 6 months and afterwards was analysed separately in the stratified analysis by tumour stage to allow for proportionality.

4.3.4 Study IV

4.3.4.1 Design

Study IV was a Swedish population-based cohort study based on data from four Swedish national health data registries: the Swedish Prescribed Drug Registry, Cancer Registry, Patient Registry, and Cause of Death Registry. The question of interest was whether use of metformin decreased the risk of developing gastric adenocarcinoma. The study participants were sampled from adult individuals (>18 years) with dispensed records of certain commonly prescribed medications between 2005 and 2015, including the medications against diabetes. Participants with a history of any cancer diagnosis or gastrectomy were excluded.

Two cohorts were constructed: a diabetes cohort and a matched cohort of common-medication users (short for 'matched cohort'). The exposure was the same in both cohorts, i.e. use of metformin. In the diabetes cohort, all cohort members were users of anti-diabetes medications and were included in the cohort at their first recorded dispensation of any anti-diabetes medication. In the matched cohort, each metformin user was included on the first dispensation date of metformin, and 10 metformin non-users were randomly sampled on the same day from the rest of common-medication users and matched with the metformin user by sex and age (± 1 year). The exposure status was allowed to change in both cohorts. The primary outcome was gastric adenocarcinoma and gastric non-cardia and cardia

adenocarcinomas were also analysed separately. The two cohorts were followed up until the occurrence of gastric adenocarcinoma, death, or the end of the study (December 31st, 2015).

4.3.4.2 Statistical analyses

Cox proportional hazard regressions were used to calculate HRs with 95% CIs, comparing the risks of developing gastric adenocarcinoma as well as gastric cardia and non-cardia adenocarcinoma among users and non-users of metformin in two cohorts. A multivariable model was applied with adjustment for seven covariates: sex, age, calendar year at inclusion (2005, 2006–2010 or 2011–2015), CCI, *H. pylori* eradication treatment, use of non-steroidal anti-inflammatory drugs (NSAIDs), and use of statins. Because no information on *H. pylori* infection was available in the four registries, *H. pylori* eradication treatment was used as a surrogate covariate for *H. pylori* infection.[108] The *H. pylori* eradication treatment was treated as a time-varying variable. Use of NSAIDs and use of statins were categorized as users or non-users and at least two dispensed records within the first year after the cohort entry were required for a participant to be identified as users of these medications.

4.3.5 Study V

4.3.5.1 Design

Study V was a Swedish population-based cohort study based on the same four Swedish registries as Study IV. The study period was from 2005 through the end of 2019. Participants who had diabetes at the time of the diagnosis of gastric adenocarcinoma between 2005 and 2018 were included in the study. The diagnosis of diabetes was based on at least one dispensed record of any anti-diabetes medication before the diagnosis of gastric adenocarcinoma. Patients with a history of any malignancy (except for non-melanoma skin cancer), or gestational diabetes, or polycystic ovarian syndrome were excluded. The exposure was metformin use within two years before gastric adenocarcinoma diagnosis. The primary outcome was death with gastric adenocarcinoma as one of the underlying causes (disease-specific mortality) and the secondary outcome was all-cause mortality. The patients were followed up from their diagnosis date of gastric adenocarcinoma until death or end of the study period, whichever came first.

4.3.5.2 Statistical analysis

Cox proportional hazard regression was used to analyse mortality outcomes between metformin users and non-users, providing HRs with 95% CIs. A multivariable model with adjustment for six potential confounders was applied. These potential confounders were sex, age at gastric cancer diagnosis, calendar year at gastric cancer diagnosis (2005-2009, 2010-2014, or 2015-2018), CCI scores, use of NSAIDs, and use of statins. The use of NSAIDs or statins was defined as at least two dispensed records within two years before the diagnosis of gastric adenocarcinoma. Four covariates were considered as potential effect modifiers and

were analysed with stratification, i.e., sex, age, tumour stage (Tis-II or III-IV), gastrectomy, and anatomical sub-locations of the gastric adenocarcinoma.

Sensitivity analyses were conducted for the risk of disease-specific mortality to test the validity of the results, including a competing-risks model, exclusion patients with metformin monotherapy, and further adjusting for insulin use. We also analysed the influences of insulin or sulfonylureas on the risk of disease-specific mortality among metformin non-users to ensure the validity. The dosage of metformin use was also analysed in relation to the risk of disease-specific mortality among metformin users diagnosed after July 1st, 2007. Total DDD of metformin intake within two years before the diagnosis of gastric adenocarcinoma was categorized into quartiles and the median values of each category were tested for trend. The proportionality assumption for Cox regression was tested by the scaled Schoenfeld residuals and was met for all analyses.

4.4 ETHICAL CONSIDERATIONS

Study II is a systematic review and meta-analysis, thus an ethical approval is not needed. For the other studies in this thesis, ethical approvals were granted by relevant authorities before each study was conducted.

The majority of the data in Study I were retrieved from the NSHDS, and an informed consent was obtained from each participant for each visit. Some data in Study I and all data in Study III-V came from Swedish national health data registries, where the data are collected during health care routines, and informed consents are exempted under the Swedish regulations. The linkage between registries was managed by the Swedish National Board of Health and Welfare and individual identifications were encrypted. The original data of the NSHDS were kept by the Umeå University and individual identifications were also encrypted. All data were stored on a safe server at Karolinska Institutet, and only a few members of the research group had the access to the data. All study results in this thesis were presented and published at an aggregated level, therefore it was impossible to identify individuals.

5 RESULTS

Main findings of the five studies are summarized in Figure 1.

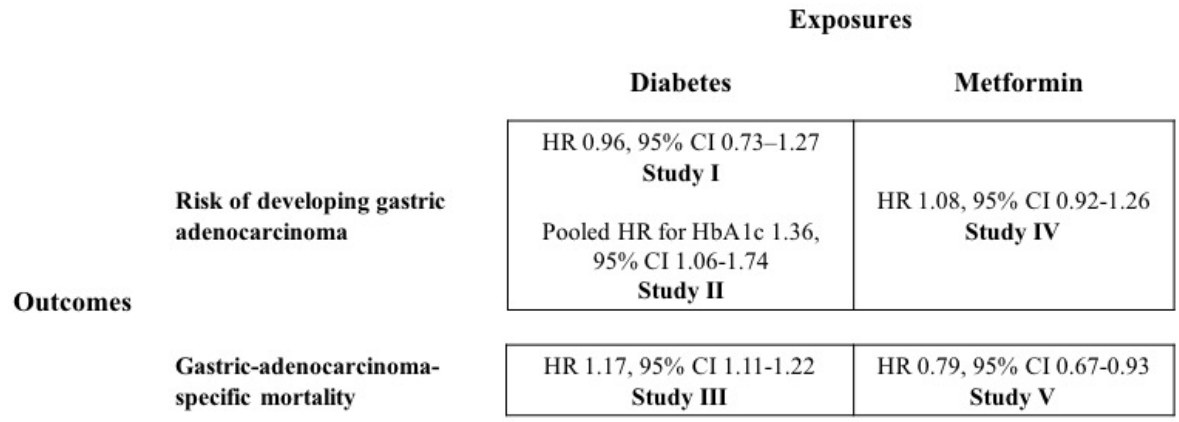

Figure 1. Main findings of Study I-V

5.1 STUDY I

Study I included 111,198 participants who were followed up for a median of 12.2 years. At inclusion, 5,958 (5.4%) participants had diabetes, 23,900 (21.5%) had prediabetes, and the remaining 81,340 (73.1%) were normoglycaemic. Table 1 presents the characteristics of participants by exposure groups at inclusion. Compared with the participants with normal blood glucose, prediabetes and diabetes participants were older, had more often BMI >27 and a shorter period of education, but were healthier in terms of smoking habits.

Table 1. Baseline characteristics of study participants

Number (%)	Normoglycaemic	Prediabetes	Diabetes
	81,340 (73.1)	23,900 (21.5)	5,958 (5.4)
Sex			
Male	40,481 (49.8)	11,023 (46.1)	3,363 (56.5)
Age, years			
<40	20,462 (25.1)	3,221 (13.5)	473 (7.9)
40 - 49	32,465 (39.9)	7,771 (32.5)	1,290 (21.7)
50 - 59	20,577 (25.3)	8,517 (35.6)	2,408 (40.4)
≥60	7,836 (9.6)	4,391 (18.4)	1,787 (28.1)
Body mass index			
≤24	31,747 (39.0)	6,025 (25.2)	866 (14.5)
24 - 27	25,233 (31.0)	6,857 (28.7)	1,212 (20.3)
≥27	24,164 (29.7)	10,947 (45.8)	3,852 (64.7)
Missing	196 (0.2)	71 (0.3)	28 (0.5)
Education level			
Compulsory school or less	14,277 (17.5)	6,159 (25.8)	2,060 (34.6)
Upper secondary school	41,298 (50.8)	11,575 (48.4)	2,729 (45.8)
College or postgraduate	25,129 (30.9)	5,917 (24.8)	1,043 (17.5)
Missing	636 (0.8)	249 (1.0)	126 (2.1)

Continued Table 1			
	Normoglycaemic	**Prediabetes**	**Diabetes**
Smoking habits			
Never smoker	15,853 (19.5)	4,830 (20.2)	1,303 (21.9)
Ex-smoker	23,027 (28.3)	7,440 (31.1)	2,036 (34.2)
Current smoker	41,435 (50.9)	11,263 (47.1)	2,475 (41.5)
Missing	1,025 (1.3)	367 (1.5)	144 (2.4)

In total, 219 participants (0.2%) were diagnosed with gastric adenocarcinoma during the follow-up. The risk of gastric adenocarcinoma was not different between participants with diabetes or prediabetes and those without (Table 2). The adjusted risk of gastric adenocarcinoma was not increased with one unit increase of either fasting blood glucose (HR 1.02, 95% CI 0.91–1.14) or post-load glucose (HR 0.98, 95% CI 0.90–1.05).

Table 2. Risk of gastric adenocarcinoma in participants exposed to prediabetes or diabetes compared with normoglycaemic participants.

	Number of GA[a]	**Crude HR (95% CI)[b]**	**Adjusted HR[b] (95% CI)[c]**
Normoglycemic	132	Reference	Reference
Prediabetes or diabetes	87	0.97 (0.74 - 1.28)	0.96 (0.73 - 1.27)
Normoglycemic	135	Reference	Reference
Prediabetes	67	1.01 (0.81 - 1.45)	1.07 (0.79 - 1.44)
Normoglycemic	132	Reference	Reference
Diabetes	17	0.83 (0.50 - 1.38)	0.77 (0.46 - 1.29)

[a] GA: Gastric adenocarcinoma

[b] Age was used as the time scale

[c] Adjusted for sex, calendar year, BMI, tobacco smoking, and education level; age was used as the time scale

5.2 STUDY II

The systematic search identified 3,473 studies. After exclusions, 5 studies reporting serum HbA1c and 7 studies reporting serum glucose were included. Of these 12 studies, 11 were cohort studies and one was a nested case-control study. Most studies came from Asia (8/12) and were based on screening programmes or health surveys (9/12). Gastric cancer was presented as one of the multiple outcomes in half of the studies, while in the other half, gastric cancer was the primary outcome. The quality assessment with Newcastle-Ottawa Scale revealed that 7 studies had moderate to high risk of bias, while 5 studies had low risk of bias.

Random-effects meta-analysis showed that elevated serum levels of HbA1c were associated with an increased risk of gastric cancer (pooled HR 1.36, 95% CI 1.06-1.74) and possibly also for serum glucose (pooled HR 1.11, 95% CI 0.98-1.26). There was moderate heterogeneity across studies reporting HbA1c ($I^2 = 43\%$, *P* in Q test = 0.43) and high heterogeneity across studies reporting serum glucose ($I^2 = 70\%$, *P* in Q test = 0.001). The subgroup analyses showed that adjustment for *H. pylori* infection may explain the

heterogeneity across studies reporting HbA1c, but not studies reporting serum glucose (Table 3).

Table 3. Subgroup meta-analyses for elevated serum levels of HbA1c and glucose in relation to risk of gastric cancer.

	Serum HbA1c			Serum glucose		
Study characteristics	**Pooled HR (95% CI)**	**$P_{Difference}$[Ω]**	**I^2 (%)**	**Pooled HR (95% CI)**	**$P_{Difference}$[Ω]**	**I^2 (%)**
Geographical area						
Asia	1.51 (1.03-2.21)	0.131	54	1.14 (0.96-1.35)	0.730	75
Non-Asia	1.14 (0.89-1.45)		7	1.08 (0.86-1.36)		71
Sex						
Male	1.08 (0.86-1.36)	0.917	0	0.99 (0.92-1.08)	0.640	0
Female	1.10 (0.71-1.69)		29.5	1.08 (0.75-1.56)		74
Assessment of risk of bias						
Moderate to high	1.14 (0.89-1.45)	0.131	7	1.09 (0.98-1.22)	0.580	88
Low	1.51 (1.03-2.21)		54	1.57 (0.44-5.63)		66
Adjustment for *Helicobacter pylori* infection						
Yes	2.08 (1.46-2.98)	0.002	0	1.57 (0.44-5.63)	0.580	66
No	1.10 (0.91-1.32)		0	1.09 (0.98-1.22)		88
Adjustment for obesity						
Yes	1.32 (0.99-1.76)	0.298	58.4	1.16 (0.96-1.42)	0.230	75
No	1.68 (0.95-2.95)		0	1.02 (0.93-1.11)		12

[Ω] *P* value in the test of subgroup difference

Asymmetry was detected in funnel plots both for studies reporting HbA1c and serum glucose, but only studies reporting serum glucose were shown by the Egger's tests to be prone to publication bias (*P* for HbA1c = 0.292; *P* for serum glucose = 0.055). The pooled HR for serum glucose was slightly attenuated after imputing the potential missing study (pooled HR 1.05, 95% CI 0.89-1.24).

5.3 STUDY III

Gastric adenocarcinoma was diagnosed in 23,591 individuals during the study period. Among them, around 12% had diabetes at diagnosis of gastric adenocarcinoma.

Gastrectomy was performed on 9,018 (38.2%) patients. The median follow-up for the total cohort was 0.59 years (interquartile range 0.18-1.75). Patients' characteristics are presented in Table 4. Patients with diabetes were slightly older and had more comorbidities than those without diabetes.

Table 4. Baseline characteristics of study patients with gastric adenocarcinoma.

	Without diabetes Number (%)	**Diabetes Number (%)**
	20,785 (88.1)	2806 (11.9)
Sex		
Male	12,752 (61)	1818 (65)
Age		
<60	3273 (16)	279 (10)
60 - 69	4339 (21)	575 (20)
70 - 79	6997 (34)	1115 (40)
≥80	6176 (30)	837 (30)
Charlson Comorbidity Index score		
0	13,645 (66)	1381 (49)
1	4937 (24)	824 (29)
≥2	2203 (11)	601 (21)
Tumour stage (from 2004)		
I-II	1488 (33)	314 (36)
III-IV	2982 (67)	560 (64)
Resectional surgery		
No	12,793 (62)	1780 (63)
Yes	7992 (38)	1026 (37)

Co-existing diabetes was associated with an increased risk of disease-specific mortality in the total cohort (adjusted HR 1.17, 95% CI 1.11-1.22) and the non-cardia sub-cohort (adjusted HR 1.17, 95% CI 1.10-1.23). The associations between diabetes and the increased risk of disease-specific mortality were pronounced among patients with no other comorbidities and who underwent gastrectomy (Table 5). The risk of all-cause mortality was increased in patients with diabetes compared with those without diabetes until 12 months after the gastrectomy (Figure 2).

Table 5. Disease-specific mortality in patients with gastric adenocarcinoma (GA) with and without diabetes, stratified by patient characteristics.

	Number of GA	Crude model HR (95% CI)	Multivariable model[a] HR (95% CI)
Charlson Comorbidity Score			
0			
No diabetes	8691	Reference	Reference
Diabetes	691	1.21 (1.14-1.30)	1.23 (1.15-1.32)
1			
No diabetes	7633	Reference	Reference
Diabetes	1086	0.92 (0.85-1.00)	0.95 (0.87-1.04)
≥2			
No diabetes	4461	Reference	Reference
Diabetes	1029	0.95 (0.85-1.06)	1.01 (0.91-1.12)
No gastrectomy			
No diabetes	12793	Reference	Reference
Diabetes	1780	1.00 (0.94-1.05)	1.04 (0.98-1.10)
Gastrectomy			
No diabetes	7992	Reference	Reference
Diabetes	1026	1.24 (1.14-1.35)	1.27 (1.16-1.38)
Tumour stage[c] I-II			
No diabetes	2982	Reference	Reference
Diabetes	560		
⩽6 months after diagnosis		1.29 (1.13-1.48)	1.26 (1.11-1.44)
>6 months after diagnosis		1.04 (0.88-1.22)	1.04 (0.88-1.22)
Tumour stage[c] III-IV			
No diabetes	1488	Reference	Reference
Diabetes	314		
⩽6 months after diagnosis		1.35 (0.95–1.94)	1.32 (0.92–1.89)
>6 months after diagnosis		1.16 (0.93-1.44)	1.09 (0.88-1.36)

[a] Adjusted for sex, age at cancer diagnosis, and calendar year of cancer diagnosis

[c] Data available in the Swedish Cancer Registry only from 2004 onwards.

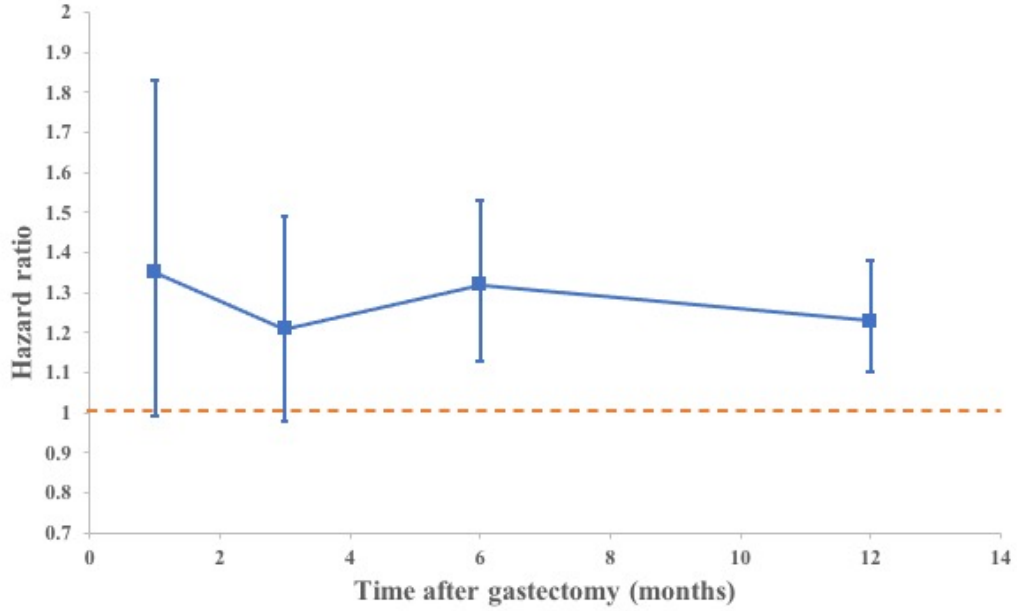

Figure 2. Risk of all-cause mortality after gastrectomy for gastric adenocarcinoma comparing patients with and without diabetes.

5.4 STUDY IV

Study IV included 544,130 participants in the diabetes cohort and 4,525,543 participants in the matched cohort. At inclusion, 61.5% of the participants of the diabetes cohort and 9.1% of the matched cohort were metformin users. The baseline characteristics of participants included in each cohort are presented in Table 6.

Table 6. Baseline characteristics of study participants in the diabetes cohort and the matched cohort.

Numbers (%)	**Diabetes cohort**		**Matched cohort**	
	Metformin users	**Metformin non-users‡**	**Metformin users**	**Metformin non-users**
Total	334,506 (61.5)	209,624 (38.5)	411,413 (9.1)	4,114,130 (90.9)
Sex				
Men	196,721 (58.8)	120,048 (57.3)	239,256 (58.2)	2,392,560 (58.2)
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 (67.9)	127,136 (30.9)	1,271,360 (30.9)
2006-2010	111,199 (33.2)	41,432 (19.7)	146,175 (35.5)	1,461,750 (35.5)
2011-2015	120,473 (36.0)	25,899 (12.4)	138,102 (33.6)	1,381,020 (33.6)
Charlson comorbidity score*				
0	250,635 (74.9)	135,583 (64.7)	303,840 (73.9)	3,265,518 (79.4)
1	59,847 (17.9)	43,510 (20.8)	75,396 (18.3)	618,631 (15.0)

Continued Table 6				
	Diabetes cohort		Matched cohort	
	Metformin users	Metformin non-users	Metformin users	Metformin non-users
≥2	24,024 (7.2)	30,531 (14.6)	32,177 (7.8)	229,981 (5.6)
Use of non-steroidal anti-inflammatory drugs or aspirin†				
No	175,589 (52.5)	109,565 (52.3)	247,988 (60.3)	3,048,169 (74.1)
Yes	158,920 (47.5)	100,059 (47.7)	163,425 (39.7)	1,065,961 (25.9)
Use of statin†				
No	162,671 (48.6)	129,555 (61.8)	22,841 (54.2)	3,377,102 (82.1)
Yes	171,835 (51.4)	80,069 (38.2)	188,572 (45.8)	737,028 (17.9)

* In the 10 years before study entry
† In the year after study entry

Participants were followed up for a median of 5.8 years, and 892 (0.1%) participants of the diabetes cohort and 6,395 (0.1%) of the matched cohort developed gastric adenocarcinoma during the follow-up. The risk of gastric adenocarcinoma and non-cardia adenocarcinoma was not decreased among metformin users compared with non-users in the diabetes cohort. The risk of gastric cardia adenocarcinoma was rather increased among metformin users compared with non-users in this cohort. In the matched cohort, metformin use was associated with an increased risk of developing gastric adenocarcinoma and its two subtypes (Figure 3).

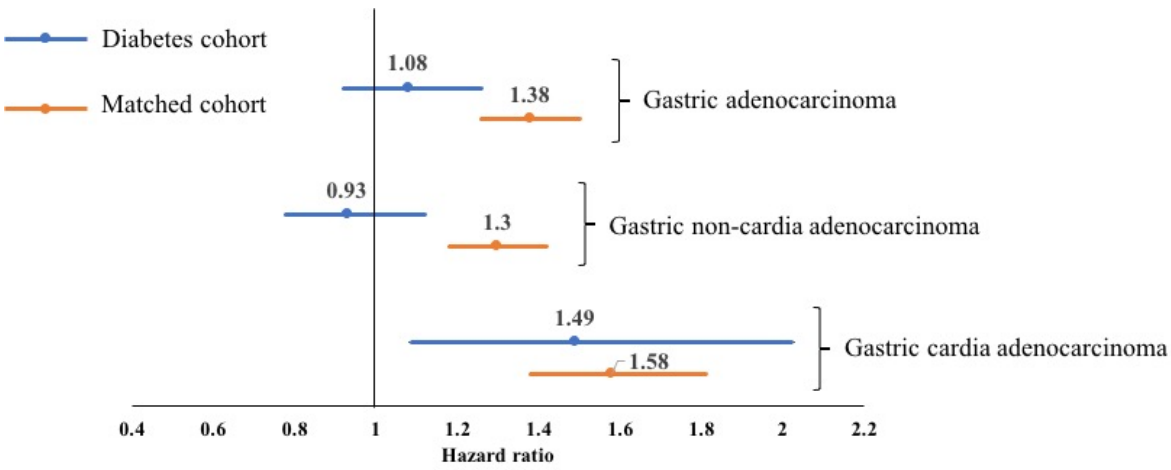

Figure 3. Risk of total, non-cardia and cardia gastric adenocarcinomas in metformin users compared with non-users in the diabetes cohort and the matched cohort.

5.5 STUDY V

Study V included 1,140 patients with diabetes and gastric adenocarcinoma. The majority (68.2%) of these patients were metformin users before the diagnosis of gastric adenocarcinoma. These metformin users were more often male, younger at cancer diagnosis, more likely to be treated with gastrectomy, and less likely to have comorbidities compared with non-users of metformin (Table 7).

Table 7. Characteristics of 1140 diabetes patients with gastric adenocarcinoma in Sweden in 2005-2018

Number (%)	Metformin users	Metformin non-users
Total	777 (68.2)	363 (31.8)
Sex		
Male	561 (72.2)	246 (67.8)
Median age (interquartile range)	72 (65-78)	75 (68-82)
Gastrectomy		
Yes	221 (28.4)	76 (20.9)
No	556 (71.6)	287 (79.1)
Charlson Comorbidity Index		
0	495 (63.7)	172 (47.4)
1	184 (23.7)	96 (26.4)
≥2	98 (12.6)	95 (26.2)

Pre-diagnosis use of metformin was associated with decreased risk of both disease-specific mortality (adjusted HR 0.79, 95% CI 0.67-0.93) and all-cause mortality (adjusted HR 0.78, 95% CI 0.68-0.90) among patients with gastric adenocarcinoma. The results were not changed dramatically in the sensitivity analyses excluding patients with metformin monotherapy (adjusted HR 0.78, 95% CI 0.64-0.96) and further adjusting for insulin use (adjusted HR 0.82, 95% CI 0.69-0.97). The analyses of the other two anti-diabetes medications showed no association between the use of these medications and risk of disease-specific mortality among metformin non-users (adjusted HR for insulin 1.14, 95% CI 0.86-1.50; adjusted HR for sulfonylureas 1.07, 95% CI 0.80-1.43). The competing-risks model showed that metformin users had a decreased risk of mortality due to both gastric adenocarcinoma and other causes compared with non-users (Figure 4). Besides, the risk of disease-specific mortality was decreased among metformin users in subgroup analyses of female sex and advanced tumour stage (Table 8).

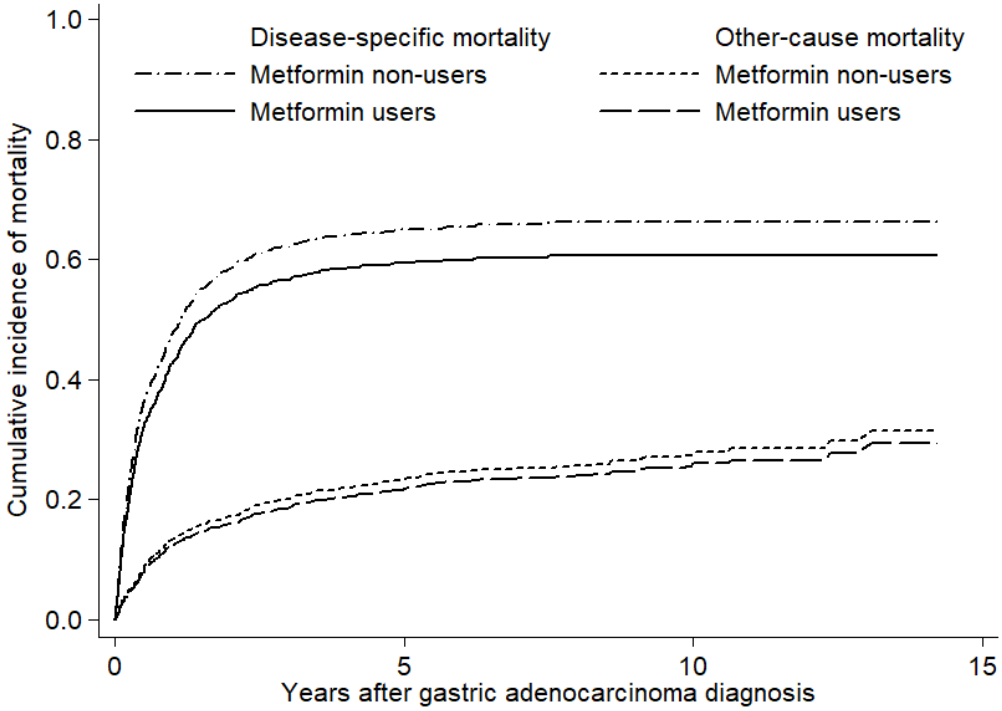

Figure 4. Cumulative disease-specific and other-cause mortality in patients with gastric adenocarcinoma and diabetes by metformin use, estimated by competing risks regression.

Table 8. Risk of disease-specific mortality after gastric adenocarcinoma diagnosis in relation to metformin use among diabetes patients.

	Disease-specific mortality		
	Number of deaths	**Crude HR (95% CI)**	**Adjusted HR (95% CI)†**
Men			
No metformin	155	Reference	Reference
Metformin	312	0.75 (0.62-0.92)	0.85 (0.69-1.03)
Women			
No metformin	87	Reference	Reference
Metformin	139	0.59 (0.45-0.77)	0.66 (0.49-0.89)
Age <73 years			
No metformin	80	Reference	Reference
Metformin	218	0.78 (0.60-1.00)	0.83 (0.64-1.09)
Age ≥73 years			
No metformin	162	Reference	Reference
Metformin	233	0.71 (0.58-0.87)	0.80 (0.64-0.99)
Gastric cardia adenocarcinoma			
No metformin	58	Reference	Reference
Metformin	127	0.70 (0.51-0.96)	0.82 (0.60-1.14)
Gastric non-cardia adenocarcinoma			
No metformin	185	Reference	Reference
Metformin	324	0.71 (0.59-0.85)	0.79 (0.65-0.95)
Tumour stage Tis-II			
No metformin	37	Reference	Reference
Metformin	78	0.73 (0.49-1.08)	0.87 (0.57-1.31)
Tumour stage III-IV			
No metformin	141	Reference	Reference
Metformin	303	0.66 (0.54-0.80)	0.71 (0.58-0.88)
No gastrectomy			
No metformin	202	Reference	Reference
Metformin	347	0.71 (0.60-0.84)	0.82 (0.68-0.99)
Gastrectomy‡			
No metformin	40	Reference	Reference
Metformin	104	0.81 (0.56-1.16)	0.87 (0.60-1.27)

† Adjusted for sex, age, calendar year of gastric adenocarcinoma diagnosis, use of non-steroidal anti-inflammatory drugs or aspirin, use of statins, and Charlson Comorbidity Index.

‡ Patients who underwent gastrectomy were followed up from the date of surgery.

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Design

In this thesis, Study I, III-V were cohort studies and Study II was a systematic review and meta-analysis. The methodological considerations are different for these two study designs.

6.1.1.1 Cohort study

A cohort study, by definition, is to identify a group of people from a study population and follow them over a certain period. These people in the cohort are classified as 'exposed' or 'unexposed'. At the end of follow-up, the occurrence of the outcomes is compared between the exposed and unexposed groups. The cohort study is a type of observational study and is levelled third in the hierarchy of scientific evidence, following systematic review and meta-analysis of randomized controlled trials (RCTs) and individual RCTs. Although RCTs are regarded superior to cohort studies, they are not always feasible due to limited resources or ethical considerations, under which conditions the cohort study is sometimes a solution balancing validity and feasibility. If well conducted, cohort studies could provide evidence to suggest (but may not prove) causation. The current thesis aimed to investigate diabetes or use of metformin in relation to the risk and prognosis of gastric adenocarcinoma. The exposures are either not possible to randomize (diabetes) or at a too early stage to launch an RCT due to limited evidence (metformin use). Therefore, cohort studies may be the optimal study design for these topics at the current stage.

6.1.1.2 Systematic review and meta-analysis

The systematic review and the meta-analysis are approaches to summarize all relevant evidence for a pre-defined research question. To achieve this aim, a systematic search is performed to find as much evidence as possible. The quality of the evidence is evaluated during the systematic review process, and the results are synthesized with statistical methods during the meta-analysis process. An important consideration of meta-analysis is the homogeneity of included studies, which not only supports the rationale to synthesize results but also guides the choice of fixed-effect or random-effects models.[109] Several systematic reviews and meta-analyses have been done to assess the association between diabetes and risk of gastric cancer.[60, 110, 111] These meta-analyses have shown high heterogeneity (I^2 ranging from 70% -95%) across the included studies, likely caused by different definitions of diabetes in individual studies, undermining the interpretation of the results. Thus, the motivation to conduct a systematic review and meta-analysis with homogenous studies shaped the choice of diabetes biomarkers as the exposure of interest for Study II.

6.1.2 Internal validity

6.1.2.1 Selection bias

Selection bias arises from the inclusion of study participants conditioning on a factor that is the common effect of the exposure and the outcome.[112] Informative censoring, volunteer bias, healthy worker bias, and pre-treatment bias are different kinds of selection biases. Because the outcomes of Study I, III-V were all identified from national registries and were virtually complete, informative censoring should not be a problem in these studies. In Study I, participants were included only if they agreed to participate and provided self-reported diabetes status or blood samples for OGTT. This volunteer-based design was potentially vulnerable to selection bias. The overall participation rates of VIP and MONICA were around 50%-60%, and 0.5% of the participants had no information on either self-reported diabetes status or OGTT results.[104, 105] However, the cancer incidence among participants of the VIP and MONICA is comparable to that of the background population, reducing the possibility of selection bias in this study.[113] In the two studies (IV and V) of which the exposure was metformin use, pre-treatment bias was possible because the studies included both new and prevalent users of metformin. The two problems related to the inclusion of prevalent users were 1) the inability to identify events that occur shortly after initiation of the therapy and 2) the inability to control for disease risk factors that might be altered by the study drugs used before the cohort entry.[114] Only the first one is a type of selection bias and such bias was not likely to exist in these two studies given the following reasons. For Study IV, the outcome was gastric carcinogenesis of which the process generally lasted for years, and thus unlikely to be an early event. For Study V, the outcome was mortality after diagnosis of gastric adenocarcinoma, and metformin users and non-users were uniformly included at their diagnosis of gastric adenocarcinoma, precluding any missing events.

6.1.2.2 Information bias

Information bias occurs if the information is not accurately collected from study participants. For categorical variables, information bias is also called misclassification. Information bias could happen for every variable within a study, but is most of a concern when the exposure or the outcome is misclassified. Misclassification can be nondifferential or differential. Nondifferential misclassification refers to the misclassification that is not related to other variables, e.g., nondifferential misclassification of the exposure is not related to the outcome. Differential misclassification means that it differs according to another variable. In study I, the exposure was identified by either self-report diabetes or an OGTT whose results showed increased glucose levels, while the unexposed participants were identified by both self-reported non-diabetes and a normal result of the OGTT. These definitions reduced the risk that participants were misclassified between the exposed and unexposed groups. In study III, the exposure was diabetes diagnosis as retrieved from the Patient Registry, where diagnoses from primary care centers were lacking. However, such misclassification should be limited because most included patients should have been hospitalized or seen at a specialist out-patient care for gastric adenocarcinoma and their diagnosis of diabetes should be thus

included in the Patient Registry. In Study IV and V, metformin is a prescription-only medication in Sweden and metformin use was based on dispensed records identified from the Prescribed Drug Registry, which should be accurate and complete. However, the dispensed records of metformin were not equal to the amounts of metformin actually taken by the patients. Hence, there is still some possible misclassification of the metformin use. Nevertheless, such misclassification is likely to be non-differential since it is not related to the outcome, i.e. occurrence of gastric adenocarcinoma or death due to gastric adenocarcinoma, and thus might only dilute the associations, but not explain them. For all cohort studies included in this thesis, the outcomes were retrieved from the Cancer Registry or the Cause of Death Registry. The accuracy of data in these two registries has been well validated (more details available in the 'Data sources' section), therefore the probability of misclassification of the outcomes is low.

6.1.2.3 Confounding

Confounding, in a simple definition, is the confusion of effects.[115] Confounding occurs when the effect of the exposure on the outcome is mixed with the effect of other variables (confounders). Thus, a confounder is the common cause (or the proxy of the common cause) of the exposure and the outcome and should not be a descendant of the exposure.[116] Confounding is the key bias that differentiates RCTs and observational studies. If the randomization process is well-performed and the trial is large enough, the RCTs are in theory exempt from confounding issues. While in observational studies, confounding only disappears when all the confounders are measured and properly dealt with, which is generally not guaranteed in practice.

In the four cohort studies of this thesis, confounding was considered with maximum utilization of the available data. In Study I, several variables were considered as potential confounders and the final selection of the six potential confounders was based on both available knowledge and the backward statistical selection. Although the selection of confounders by the statistical model is generally not recommended,[117] a trade-off has to be made between sufficient adjustment for confounders and preservation of statistical power. Among potential confounders that were not adjusted for in this study were *H. pylori* infection and the use of medications, e.g. statins and metformin, which were not available in the dataset. However, whether *H. pylori* infection is associated with diabetes is not well-established and the majority of the exposed patients were exposed to prediabetes for whom drug treatments are usually not needed.

In Study IV, the data on *H. pylori* infection was also lacking, but *H. pylori* eradication treatment was adjusted for as a surrogate for *H. pylori* infection. The results of the matched cohort in this study were believed to be influenced by confounding by diabetes, thus the results of the diabetes cohort were more valid. The increased risk of gastric cardia adenocarcinoma among metformin users in this study may be explained by unmeasured confounding by obesity, which is one of the major weaknesses of this study. With the method proposed by Tyler et al.,[118] an unmeasured confounder that was associated with both the

metformin use and gastric cardia adenocarcinoma by a relative risk of 2.3 was sufficient to explain the increased risk, and adjustment for an unmeasured confounder by a relative risk of 1.4 could lead to the adjusted 95% CI to include 1. According to the literature, diabetes patients taking metformin were two times more likely to be obese compared with other diabetes patients,[94] and the relative risk of obesity in relation to the risk of gastric cardia cancer varies between 1.4-3.0.[119] This indirect evidence supports a role of confounding by obesity in this study.

In Study III and V, lifestyle factors such as smoking or physical activity might also act as potential confounders, but were not available in the dataset. However, the influence of these factors on the prognosis of gastric adenocarcinoma should be limited compared with that of the tumour stage or gastrectomy, and should thus not introduce substantial confounding bias even if not adjusted for. Besides, based on the knowledge acquired in Study III that diabetes worsened the prognosis of gastric adenocarcinoma, the study patients of Study V were restricted to diabetes patients, which counteracted the confounding by diabetes in this study.

Despite the above-mentioned efforts, unmeasured or residual confounding always exists in observational research, including each of the cohort studies in this thesis.

6.1.2.4 Bias related to pharmacoepidemiology studies

Immortal time bias is common in pharmacoepidemiology studies and may influence the validity of the study results.[32] Immortal time bias arises when the unexposed time is mistakenly classified as the exposed time (or vice versa), and could thus distort the associations.[120] In Study IV, this bias was avoided by the inclusion of participants at their first dispensation date of anti-diabetes medications in the diabetes cohort and matching on the same entry day in the matched cohort. Additionally, the exposure status was allowed to change in this study. In Study V, this bias was not a problem because participants were included uniformly at their diagnosis date of gastric adenocarcinoma.

Another common bias inherent in pharmacoepidemiological studies is confounding by indication, i.e. the indication for the treatment also affects the occurrence of the outcome. Thus, the observed association between the treatment and the outcome could partly be attributed to the indication for which the treatment is prescribed. Confounding by disease severity is a subtype of confounding by indication[121] and is possible in Study IV and V since the comparison is made between metformin, a first-line treatment for diabetes, and other anti-diabetes treatments. The adjustment for use of statins might partly counteract this bias. Since statin is used for the prevention or treatment of macrovascular diseases, which are common morbidities of diabetes, the use of statin could reflect diabetes severity to some extent.[122] Besides, the null association found in Study IV was not likely to be explained by this bias because such bias would distort the associations towards the opposite direction. In Study V, this bias was addressed in the sensitivity analysis that further adjusted for insulin use and the risk estimate was not changed.

A third common problem was bias due to time lag and latency which may occur when the effect of a first-line treatment is compared with second- or third- line treatments.[32] It is possible that due to the long latency of the outcome, the effect of the first-line treatment on the outcome is observed during the exposure period of the second-line treatment. Such bias is plausible for metformin studies because almost all drug treatments for type 2 diabetes start from metformin. In Study IV, the influence of this potential bias was partly removed in the sensitivity analysis excluding gastric adenocarcinoma occurred within the first year of follow-up. While in Study V, a two-year exposure window was used and the exposure status was not allowed to change after the inclusion, decreasing the possibility of this bias.

6.1.2.5 Bias in the systematic review and meta-analysis

A systematic review and meta-analysis of RCTs is usually acknowledged as the highest level of scientific evidence, but doubts have been posed on which evidence level a systematic review and meta-analysis of observational studies should locate. The major concerns are the lower internal validity of observational studies compared with RCTs, and the difficulty to assess the risk of bias both within and across studies.[123] In the systematic review and meta-analysis of this thesis, combined efforts were made to minimize this problem, including following a pre-defined protocol, critically assessing the quality of the included studies, and reporting the results according to the guidelines.[124, 125]

Another concern on systematic review and meta-analysis is potential publication bias, mainly caused by the differential publication of studies reporting relatively large effects or including large sample sizes.[126] In other words, small studies with null or weak effects are less reported and might thus not be included in the meta-analysis. A preliminary method to assess publication bias is through checking the asymmetry of funnel plots (Figure 5). The funnel plots of serum glucose showed that a small study reporting a strong association was included, while on the opposite side, small studies might be missing. On the other hand, the funnel plots of HbA1c showed inclusion of a small study reporting null association, while small studies reporting strong associations might be missing. Therefore, although asymmetry was identified in both plots, studies reporting serum glucose were more prone to publication bias, which was also shown by the results of the Egger's test. As expected, the pooled association between serum glucose levels and risk of gastric cancer weakened after trim-and-fill imputation, again indicating the potential missing studies.

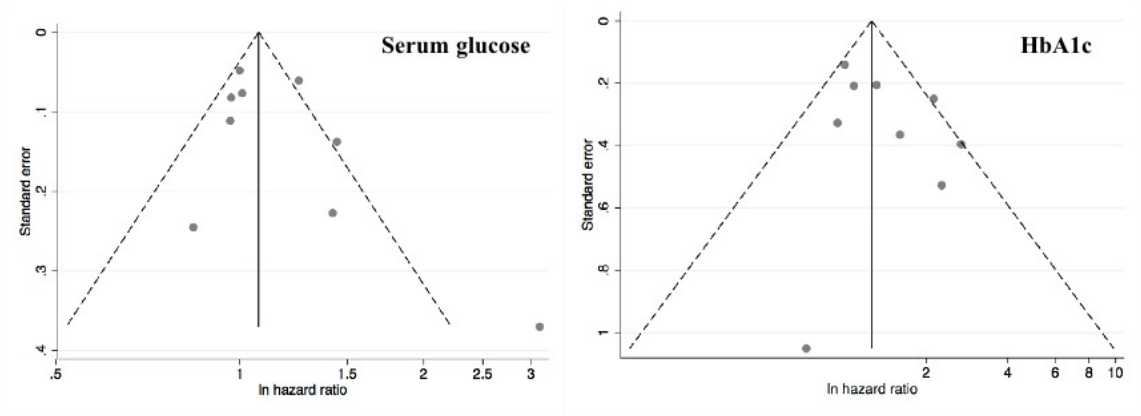

Figure 5. Funnel plots for studies reporting serum glucose and HbA1c.

6.1.3 Random error

While different biases are regarded as systematic errors that influence the internal validity of study results, random error is regarded another problem that alters the precision of study results. Random errors are inevitable and unpredictable, but could be reduced by increasing the sample sizes. In this thesis, Study III-V were based on nationwide cohorts, which helped to decrease random errors. The meta-analysis in Study II was another way to increase sample sizes by combining results from several studies. However, when conducting subgroup analysis, the sample size is usually divided into several parts and the risk of random error increases.

Two types of errors may occur in the statistical assessments, i.e., type I error (false positive) and type II error (false negative). Type I error occurs when a true null hypothesis is rejected. Under the null hypothesis, an event has a certain probability called *P*-value of the significance of the test. The *P*-value is usually compared to a predetermined cut-off called the level of the test, which is empirically set at 5% for a single test. If the *P*-value is lower than that level, the null hypothesis is rejected. Although the *P*-value has a long history, the use has been discouraged by many scientists.[127-129] Alternatively, 95% CIs can be used. The 95% CI is an interval estimation and could be interpreted as to be 95% confident that the true value of the population is included within this interval. The 95% CIs were used throughout the studies in this thesis as they informed not only statistical significance, but also the precision and direction of the associations.[130] A common source of type I errors is multiple testing. In this thesis, we reduced the number of tests by strictly following detailed and pre-defined study protocols for all studies. Type II error, on the other hand, occurs when the null hypothesis is not rejected but a true alternative value exists. The complement to the probability of type II error is called power, and the power can be increased by enlarging the sample size, improving the efficiency of statistical methods, reducing the variability in the sample, or looking for larger differences between the null and the alternative hypotheses. From a post hoc point of view, Study I might be underpowered for the reason that it was based on countywide cohorts and the incidence of the outcome (gastric adenocarcinoma) was rare. Another explanation might be that the true difference between the exposed and unexposed was small that could not be detected under this sample size.

6.1.4 External validity

The external validity, or generalizability, of a study is the possibility to extrapolate the results to another population. This is often an advantage of cohort studies over RCTs because the results of cohort studies may be easily applied to real-world settings, while the results of RCTs are usually based on highly selected and homogenous populations. However, internal validity is the precondition of external validity and always overweighs the value of external validity. In general, the results of Study III and V are less likely to be severely influenced by different errors and thus are credited with higher external validity. However, given that the results of Study III and V were based on a single population and that the sample sizes were not large enough for robust stratification analyses, the results might only be generalized to populations that are similar to the Swedish population.

6.2 GENERAL DISCUSSION

6.2.1 Strengths and weaknesses

Shared strengths of Study I, and III-V are the population-based cohort design, complete follow-up, and adjustment for several potential confounders. Moreover, whenever possible, gastric non-cardia and cardia adenocarcinomas were analysed separately. A major weakness of these studies was the lack of information on some potential confounders as discussed above. Besides, the information on some potential effect modifiers, e.g. neoadjuvant therapy in Study III and V, was also not available. The strength of the systematic review and meta-analysis includes the well-defined research question, quality assessment of included studies, as well as assessment of publications bias. Furthermore, Study II might be the first study quantitively synthesized the association between objectively measured serum levels of HbA1c or glucose and the risk of gastric cancer. Yet, the weakness of this study was the limited number of studies and the unexplained heterogeneity across studies reporting serum glucose.

6.2.2 Study I, II and IV

The results of Study I showed that prediabetes or diabetes did not increase the risk of developing gastric adenocarcinoma. On the other hand, the results of Study II (a systematic review and meta-analysis) showed that serum HbA1c, and presumably serum glucose also, were associated with an increased risk of gastric cancer. In general, the evidence grade of a systematic review and meta-analysis is considered higher than that of a single cohort study. The explanations for the seemly contradictory results between Study I and II might be the lack of statistical power in Study I (type II error) or differences in study designs and study populations (Study I: Swedish population, and Study II: multiple populations of which most were from East Asia). Another factor that may contribute to the results of Study I was that the VIP, where the majority of the participants came from, was originally designed as an

individual-tailored health promotion program aiming to reduce the morbidity and mortality from cardiovascular disease and diabetes. The evaluation of this program showed that it reduced all-cause and cardiovascular mortality among the participants.[131] Thus, factors associated with both cardiovascular death and gastric adenocarcinoma (e.g. smoking habits) might have been changed due to the intervention during the follow-up. Although the exposure status of diabetes or prediabetes was allowed to change in Study I, the confounders were adjusted only by their baseline values. Therefore, it is possible that some time-varying factors, measured or unmeasured, were not fully accounted for in this study.

Dependence on exposure duration might partly explain why in Study II, serum HbA1c levels were associated with an increased risk of gastric cancer, but the association was less evident for serum glucose levels. This finding was also supported by another study showing that only the trajectory pattern of elevated serum glucose that lasted for a long period was associated with an increased risk of gastrointestinal cancer.[132] Previous systematic reviews and meta-analyses that investigated diabetes in relation to the risk of gastric cancer showed inconsistent results and there was high heterogeneity across the included studies.[60, 110, 111, 133, 134] The inclusion of only studies reporting serum biomarkers reduced the heterogeneity in the analysis of HbA1c. Why high heterogeneity remained in the analysis of serum glucose could be attributed to the different categorizations of glucose levels in the included studies, and the synthesis of results of both fasting and non-fasting serum glucose. An optimal solution would be analysing fasting and non-fasting serum glucose separately and only combining studies with similar categorizations, but this was not possible because of the limited number of studies. An interesting finding in the meta-analysis of studies reporting HbA1c was the different pooled estimates in studies that adjusted for *H. pylori* infection and those that did not. *H. pylori* infection is a known risk factor for gastric cancer, but its association with diabetes or hyperglycaemia is not well understood. Therefore, whether *H. pylori* infection is a confounder or effect modifier in the associations between hyperglycaemia and gastric cancer should be explored in future studies.

The results of Study IV showed that use of metformin did not decrease the risk of gastric adenocarcinoma, which was consistent with some previous studies,[93, 135] but not others.[91, 92] A recent systematic review and meta-analysis showed decreased risk of gastric cancer associated with metformin use only among Asian populations, but not Western populations.[96] Thus, population differences might partly explain the different results between Study IV and some other studies. When designing Study IV, the construction of the matched cohort was based on the knowledge obtained from previous Study I, i.e. that diabetes might not influence the risk of gastric adenocarcinoma. However, the distinct results found in the matched cohort and diabetes cohort suggest an association between diabetes and the development of gastric adenocarcinoma, further supporting the findings of the systematic review and meta-analysis (Study II). In other words, diabetes was likely a confounder or closely correlated with a confounder in the association between metformin use and risk of gastric adenocarcinoma. Hence, the results of the diabetes cohort were probably less prone to confounding bias. The still significant association between metformin use and increased risk of gastric cardia

adenocarcinoma after restriction to diabetes patients could be potentially explained by confounding by obesity as discussed above.

6.2.3 Study III and V

Both Study III and V were based on patients diagnosed with gastric adenocarcinoma in Sweden. The exposures were co-existing diabetes (Study III) and metformin use (Study V) before the diagnosis of gastric adenocarcinoma. The primary outcome was disease-specific mortality in both studies. The results of Study III showed co-existing diabetes was associated with a worse prognosis in gastric adenocarcinoma, and this association was most pronounced in patients who underwent gastrectomy. This might be due to that patients who underwent gastrectomy had a longer period of survival than those who did not, which allowed the influence of co-existing diabetes to be observed. Hyperglycaemia might play a role in the associations between diabetes and increased risk of mortality in gastric adenocarcinoma. Diabetes patients are more vulnerable to glucose turbulence than non-diabetes individuals under certain stress such as gastrectomy, and poor glycaemic control is associated with an increased risk of postoperative mortality.[136-138]

Based on the results in Study III that diabetes increased the risk of mortality in gastric adenocarcinoma, Study V was designed among diabetes patients only to avoid confounding by diabetes. The results of Study V showed pre-diagnosis use of metformin was associated with better survival in gastric adenocarcinoma. This finding was supported by four previous studies,[139-142] while the results from two other studies were not consistent.[143, 144] The number of patients included in Study V was more than any of these six studies. Different mechanisms may explain the protective role of metformin in the prognosis of gastric adenocarcinoma, including a direct influence on the tumour-related pathways,[145] an indirect influence on balancing glucose and insulin levels,[31] and a synergistic influence with chemotherapy.[146] However, the glycaemic control among metformin users should not be better than that of patients using other anti-diabetes medications,[139] suggesting that the glucose-lowering function may not be the main mechanism of metformin to decrease the mortality. The associations between metformin use and decreased mortality in gastric adenocarcinoma was pronounced among patients with more advanced tumour stage. Since patients with advanced tumour stage are usually treated with chemotherapy, the associations found in this subgroup support the mechanism of an integrated influence of metformin and chemotherapy agents.

7 CONCLUSIONS

- Elevated serum levels of HbA1c might increase the risk of gastric cancer.
- Diabetes may increase the risk of disease-specific mortality among patients diagnosed with gastric adenocarcinoma.
- Metformin use may not prevent gastric adenocarcinoma among diabetes patients.
- Pre-diagnosis use of metformin may reduce the risk of mortality in gastric adenocarcinoma among diabetes patients.

8 FUTURE PERSPECTIVES

The associations between diabetes or its biomarkers and the risk of gastric adenocarcinoma should be further investigated in future studies, especially in western populations. The role of other factors, e.g. sex, ethnicity, or known risk factors of gastric cancer, in the association between diabetes and gastric carcinogenesis is not clear and large population-based studies are needed. Although the existing evidence may suggest that individuals with poor glycaemic control have a higher risk of developing gastric adenocarcinoma compared with those of normoglycaemia, whether they can benefit from stricter glycaemic control is not known. For RCTs of which diabetes medications are the intervention and intermediate glucose metabolism is measured, secondary analyses for gastric adenocarcinoma incidence may help to elucidate this question, given the follow-up is long enough and the sample size is adequately large.

Diabetes might worsen the prognosis in gastric adenocarcinoma after gastrectomy, but whether intensive perioperative glucose management could improve the survival in gastric adenocarcinoma is not clear. RCTs have found that intensive glucose control decreases morbidity, but not mortality among surgical patients with diabetes.[147, 148] Since intensive glycaemic control may increase the risk of lethal hypoglycaemia, careful serum glucose management during the perioperative period among patients with gastric adenocarcinoma is needed and both benefits and risks should be taken into account.

Future studies aiming to analyse the role of metformin use in the development of gastric adenocarcinoma should restrict the study population to diabetes patients and separately analyse gastric cardia and non-cardia adenocarcinoma. Moreover, confounding by obesity should be considered during the study design.

Although metformin use may be associated with improved survival among diabetes patients with gastric adenocarcinoma, whether this association is possible to extrapolate to non-diabetic individuals is not known and well-designed cohort studies are needed. Future studies should also explore if the association varies for different doses, duration, and timing of metformin use. Currently, the evidence is far from enough to support an RCT of metformin as a therapeutic agent for gastric adenocarcinoma patients.

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11 SUPPLEMENTS

Supplementary Table 1. Codes for identifying covariates in different Swedish health data registries.

Covariate	Version	Codes
The Swedish Cancer Registry		
Adenocarcinoma	WHO/HS/CANC/24.1	096, 196
Any cancer (excluding non-melanoma skin cancer)	ICD-7	140-209, excluding 191
Gastric cancer	ICD-7	151
Gastric cardia cancer	ICD-7	151.1
The Swedish Patient Registry		
Diabetes	ICD-9-SE	250
Diabetes	ICD-10-SE	E10-E14
Gestational diabetes	ICD-10-SE	O24.4 and O24.9
Gastrectomy	before 1997	4411-4420, 4422, 4424-4426, 4429, 4430, 4432, 4434, and 4435
Gastrectomy	After 1997	JDC and JDD
Polycystic ovary syndrome	ICD-9-SE	256E
Polycystic ovary syndrome	ICD-10-SE	E28.2
The Swedish Cause of Death Registry		
Gastric cancer	ICD-9	151
Gastric cancer	ICD-10	C16
Oesophageal cancer	ICD-10	C15
The Swedish Prescribed Drugs Registry		
H. pylori eradication package	ATC	A02BD
Insulin and analogues	ATC	A10A
Metformin	ATC	A10BA02
Metformin included in the combined medication	ATC	A10BD02 A10BD03 A10BD05 A10BD07 A10BD08 A10BD10 A10BD11 A10BD13 A10BD14 A10BD15 A10BD16 A10BD17 A10BD18 A10BD20 A10BD22
Non-steroidal anti-inflammatory drugs	ATC	M01A, N02BA, B01AC06 C10BX01 C10BX02 C10BX04 C10BX05 C10BX06 C10BX08 C10BX12 C07FX02 C07FX03 C07FX04
Oral glucose lowering drugs	ATC	A10B
Statins	ATC	C10AA, C10B
Sulfonylureas	ATC	A10BB